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Pain in Women

A Clinical Guide

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Preface

It was during my first clinical rotation of my medical school experience when I met Marilyn. She was a white woman in her 50's who had come into the Emergency Department (ED) for the third time in the last 2 months complaining of severe abdominal pain. Her husband, a truck driver, was on the road frequently, and she had called an ambulance due to the severity of the pain. I was working on the Internal Medicine service at the time. She was admitted to our care for a full diagnostic work-up, having been sent away during the two prior ED trips with some pain medication and advice to follow up with her primary care physician. When my resident evaluated her with me in tow, she was writhing on the gurney with tears in her eyes; her distress was palpable before even touching her belly. After a brief examination, my resident supervisor took me aside and explained how she was the perfect example of the "hysterical female patient". She was clearly either "drug-seeking" or "attention-seeking" or possibly both, probably due to her husband's long stints away from home. Two days later, a large cancerous mass was found in her proximal colon (a location typically missed in those days by the commonly performed sigmoidoscopy that imaged only the distal portion).

This experience shaped the remainder of my medical school and residency training. I became sensitized to how women and men experience and express pain and medical symptoms differently, how these symptoms are then interpreted by medical professionals, and how these interpretations may be translated into differing diagnostic testing, recommendations, and interventions. Perhaps more importantly, I wondered at the easily observable sex differences seen in the clinic and at how readily the majority was attributed solely to psychological factors. I was fascinated by the beautiful renderings in our anatomy atlas that largely depicted male examples (except where explicitly illustrating the female sex organs). On the one hand, biological and anatomical differences between the sexes seemed all too obvious, and yet no one seemed willing to recognize the clinical implications of these differences in a sophisticated and satisfying way. The idea of "Women's Health", now a popular catchphrase in medicine, was an unfamiliar term at that time.

In 2001, the Institute of Medicine (IOM) issued a report entitled "Exploring the Biological Contributions to Human Health: Does Sex Matter?" that identified the

study of sex-based differences in human health conditions as an important area for future research. In 2007, the International Association for the Study of Pain (IASP) declared the Global Year Against Pain in Women. This was a timely declaration that marked the increasing recognition of the important differences between the sexes when it comes to pain. Over the prior decade, the body of knowledge regarding sex differences in pain conditions has grown considerably. The fact that strong sex differences exist when it comes to pain is now a well-recognized phenomenon within the field of Pain Medicine. Yet, our knowledge of the implications of these differences, particularly how to translate these findings into better treatment of pain in both sexes, remains in its relative infancy. The literature is difficult to interpret and often more accessible to the basic science researcher than to the clinician treating patients with pain conditions. Among the IASP's 2007 consensus report recommendations on sex and gender differences in pain were those aimed at making future sex, gender, and pain research more easily interpretable in order to advance this field of study and increase its clinical applicability.

The aim of this text is to review the basics of our current understanding regarding the biological differences between the sexes when it comes to pain conditions. We hope to provide clinicians in varying fields with a guide that will help elucidate the proposed neuroanatomical and neurophysiological mechanisms that are currently understood to underlie these differences. Women are affected by many chronic pain conditions in overwhelmingly greater numbers than are men and are also at higher risk of disability due to pain in all age groups. Therefore, this text reviews in detail pain conditions commonly encountered in women with their recommended treatments. In addition, special considerations in certain populations of female patients with pain, such as the female athlete, those who are pregnant, postpartum, and experiencing menopause, and survivors of breast cancer, are discussed. A special chapter is dedicated to the issue of early life trauma and chronic pain, the goal here being to clear misconceptions and elucidate the biological mechanisms believed to play a role in this phenomenon. Finally, an entire chapter is devoted to discussion of the role that physical therapy plays in the treatment of pelvic pain. In our experience, this is a little-known branch of physical therapy that, yet, has much to offer to patients with pelvic pain disorders.

As mentioned above, we realize there is much to be learned about sex differences in pain and, even as this book is submitted for publication, further research is being published in this arena. However, we believe the need for this text outweighs the cautionary tendency of awaiting further evidence before its creation. Ultimately, we desire this text to increase the confidence of the clinician treating women with pain disorders and improve the treatment of pain in women at all life stages.

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Contents

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Chapter 1
Sex Differences in Pain

Allison Bailey

Introduction

Women are affected by chronic pain and painful conditions of the musculoskeletal system in overwhelmingly greater numbers than are men [1, 2]. Those occurring with higher incidence in women include migraine headache, fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, chronic pelvic pain, interstitial cystitis, carpal tunnel syndrome, patellofemoral pain syndrome, deQuervain's tenosynovitis, and rheumatoid arthritis [3]. Women are also at greater risk of joint pain due to arthritis [4] and of developing pain-related disability [5]. However, when surveying all types of pain, there does not appear to be a clear female predominance in either the prevalence or severity of chronic pain [6]. Despite these findings, women have been reported to experience more recurrent and widespread pain or pain at multiple body regions [7]. These findings suggest that the differences in pain modulation observed between the sexes may be more qualitative than strictly quantitative.

The 2001 Institute of Medicine (IOM) report "Exploring the Biological Contributions to Human Health: Does Sex Matter?" identified the study of sex-based differences in human health conditions as an important area for future research [8]. These recommendations were later expanded by an interdisciplinary group gathered by the Society for Women's Health Research to provide specific guidelines for conducting research on sex differences [9]. Evidence that sex and gender strongly influence the experience of pain is increasingly emerging within the field of pain medicine. The fact that there are sex differences when it comes to pain, both of a clinical and experimental nature, is now a well-recognized phenomenon. However, defining and explaining these differences is still being studied.

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At the outset, terminology should be clarified. With regard to pain, the terms sex and gender are often used interchangeably. However, the term “sex” should be used to refer to the biological difference of an individual being male or female. Gender, on the other hand, has to do with learned social behaviors and the extent to which they are defined as masculine or feminine. For example, women are traditionally expected to demonstrate a greater willingness to report painful symptoms than are men. There is evidence that such gender role expectations strongly influence pain behavior [10]. However, there is now substantial data that hormonal variables and other biological differences between men and women play an important role in pain modulation. It is likely, therefore, that learned social behaviors and psychosocial factors interact with and are expressions of biological differences that result in the observed variations in expression of pain.

Recognition of the key differences between men and women when it comes to pain is necessary to provide optimal care to women with both subacute and chronic pain and musculoskeletal disorders. Pregnancy, labor and delivery, the hormonal fluctuations of the menstrual cycle, and the decrease in gonadal hormones that accompany menopause may all affect the musculoskeletal and neurological systems in varied and complex ways that may result in painful conditions. Again, the precise mechanisms of these pain differences remain under investigation. Nevertheless, clinicians caring for women throughout their lifespan must be equipped to address their needs with a variety of pain and musculoskeletal issues. This chapter will provide an introduction to the sex differences in pain modulation now believed to be important, with the goal of proving further insight into the specific pain conditions covered in this chapter. Implications for sex-specific treatment of pain will also be discussed. However, further research in this area is needed before definite recommendations can be made.

Background

Despite the widespread popular belief that women are better able to tolerate pain due to the fact that they endure childbirth, laboratory studies of experimentally induced painful stimuli have repeatedly demonstrated that women, in fact, have lower pain thresholds and lower pain tolerances than men [7, 11]. The magnitude and consistency of these findings, however, have been shown to vary based on the type of experimental pain stimulus used. In a meta-analysis of studies examining sex differences in experimental pain, moderate to large effect sizes were found for the various stimuli, with pressure pain being the most consistent and showing the largest effect sizes and thermal pain being the least consistent in demonstrating sex differences in pain responses [12]. It is particularly intriguing that the strongest sex differences are demonstrated for pressure. Tenderness to pressure palpation is frequently used in clinical practice to evaluate pain of the musculoskeletal system and, in fact, is the main tool used to diagnose fibromyalgia syndrome (FMS), a clinical pain condition with a strong female predominance.

These sex differences in pain responses also extend to more sophisticated experimental measures. For example, women exhibit greater temporal summation of thermal pain, as compared to men [13]. In addition, women, but not men, with temporomandibular joint disorder (TMD) demonstrate significantly greater temporal summation of mildly noxious mechanical stimuli applied to the fingers [14]. Temporal summation of pain, or wind-up, is also known to occur in fibromyalgia patients, the majority of whom are female [15, 16].

Temporal summation is the observable manifestation of the process of wind-up, a central nervous system (CNS) condition during which a repetitive peripheral nociceptive input becomes amplified (rather than inhibited) at the level of the dorsal horn of the spinal cord. The second-order neurons responsible for this condition are referred to as wide dynamic range (WDR) neurons due to their ability to respond to repeated stimulation with an increasingly robust response; this can eventually lead to spontaneous activity within the neuron that is independent of peripheral stimulation (long-term potentiation). This process was first known to occur within the hippocampus due to its involvement in memory formation: this type of recurrent activity facilitates connections that ultimately produce memory in the brain. When this same neurobiology occurs within the dorsal horn of the spinal cord, a "pain memory" is formed that is independent of peripheral stimulation [17]. The fact that this process occurs to a greater extent in women suggests a potential hormonal influence on a vital neurobiological process underlying the development of sustained pain states.

Menstrual Cycle Variations and Pain

A substantial body of research examining the influence of the gonadal hormones on pain is that of menstrual cycle variations and pain sensitivity. Several of the most common clinical pain conditions in women have been shown to vary in frequency and severity of symptoms based on menstrual cycle phase. Many of these conditions occur most commonly during the reproductive years, and some abate during the postmenopausal time period. The most well-known and well-studied of these conditions is menstrual migraine, which occurs during the premenstrual phase of the cycle when estrogen levels are rapidly declining (see Chap. 8). In addition, symptoms attributable to fibromyalgia, interstitial cystitis, irritable bowel syndrome, and even rheumatoid arthritis have been reported to fluctuate with the menstrual cycle.

Multiple studies have examined changes in pain sensitivity across the menstrual cycle with sometimes conflicting results. Among the methodological problems with these studies is the manner in which cycle phase was determined. In the majority of studies, this was done by self-report of the subject of the first day of the last menstrual period. This not only has the inherent problem of recall bias but also fails to account for intersubject variation in the day of ovulation, which makes it difficult to precisely determine phase by this method. Surprisingly, few studies attempted to measure hormone levels in order to determine phase. In addition, menstrual phase in many

studies was statically described as either estrogen dominant (the follicular phase) or progesterone dominant (the luteal phase). In fact, great fluctuations in hormone levels occur over the course of both the follicular and luteal phases. For example, the mid-luteal phase, which is characterized by relatively high levels of progesterone, is hormonally quite different from the late-luteal (or premenstrual) phase when both estrogen and progesterone levels are rapidly falling and is the time period known to be associated with various psychological and physiological symptoms. Few of these studies, unfortunately, attempted to distinguish this time period from the remainder of the luteal phase.

However, Riley and colleagues performed a meta-analysis, attempting to clarify the available data. This revealed significant differences in pain sensitivity across the menstrual cycle with the findings varying based on the type of experimental pain stimulus that was applied [18]. For the majority of stimuli used, there was less pain sensitivity during the follicular phase of the cycle. However, for electrical stimulation, the pattern reversed itself, showing less pain sensitivity in the luteal, or progesterone-dominant, phase, with small to moderate effect sizes seen for all. These results raise the question of what type of experimental pain stimulus is most clinically relevant. Pressure as an experimental pain stimulus seems important to study, since tenderness to pressure palpation is frequently used in clinical practice to diagnose pain conditions and because of the strong sex differences observed for pressure palpation experimentally.

On closer review, only two of the studies in the above meta-analysis looked at response to pressure palpation as a pain stimulus. One study compared pain responses in the mid-follicular phase of the cycle to the premenstrual (late luteal) phase [19], and the other compared the periovulatory (late follicular phase) to the menstrual and premenstrual phases [20]. Therefore, neither examined responses in the mid-luteal phase of the cycle when progesterone levels are highest. This raises some concern about the conclusion that pressure pain sensitivity is higher during the luteal phase of the cycle.

Another study not included in this meta-analysis examined sensitivity to pressure pain across the menstrual cycle in a slightly different way. Tender point count by palpation was measured at 13 spots bilaterally in 36 women with normal menstrual cycles and 30 oral contraceptive users with correlation made to menstrual cycle phase as determined by self-report. The number of tender points to palpation was significantly greater during the follicular (estrogen dominant) phase of the cycle than during the luteal (progesterone dominant) phase of the cycle in the women with normal menstrual cycles. No significant variations in tender point count were noted in users of oral contraceptives [21]. This study suggested that normally cycling women may be less vulnerable to pressure pain stimuli during the mid-luteal phase of the menstrual cycle when progesterone levels are relatively high.

Recently, pain thresholds for cold, heat, pressure, and electrical current were measured in 24 healthy, normally menstruating women on days 1, 4, 14, and 22 of the menstrual cycle [22]. Salivary samples were collected to measure levels of 17-beta-estradiol, progesterone, and testosterone. Significant variations in pain thresholds were noted for cold, pressure, and electrical current. The highest

pain thresholds were found on day 22 for pressure and electrical stimuli with cold peaking on day 14. Pain thresholds did not correlate with salivary hormone levels except for testosterone and electrical pain threshold on day 1. Further research in this area is clearly needed to better elucidate the influence of menstrual cycle fluctuations on pain responses. For the majority of chronic pain conditions affecting women, such as those discussed in more detail later in this chapter, careful tracking of menstrual cycle phase may provide further insight into otherwise unexplained exacerbations of pain and related symptoms.

Gonadal Hormones and Pain

Basic science research is helping to elucidate how specific gonadal hormones may influence pain responses. Many animal studies, mainly in rats, have demonstrated fluctuations in pain threshold which correlate with specific hormonal changes. For example, female rats demonstrate higher rates of hindpaw licking (a commonly studied pain behavior in rats) in response to formalin injection (an experimental model of inflammatory pain) than do males. However, when male rats are administered estradiol, their hindpaw licking increases to levels equivalent to females [23], suggesting a potential pronociceptive role of estradiol. However, multiple studies in rats have demonstrated increased latency to respond to acute nociceptive input (higher pain threshold) in ovariectomized rats treated with estradiol as compared to their hormone-depleted counterparts [24].

In addition, gonadectomized male rats show decreased ability to adapt to painful stimuli as compared to normal males [25]. Hormonally, gonadectomized male rats have lower levels of testosterone and higher levels of estradiol as compared to their intact counterparts. When formalin injections were administered to intact and gonadectomized male rats once a week for 3 weeks, intact male rats demonstrated decreasing pain behavior with repetitive injections. Gonadectomized male rats, on the other hand, continued to demonstrate high levels of pain behavior without adaptation. Associated with this, gonadectomized males also showed increased levels of c-FOS gene expression in the central nervous system (CNS), changes that were not observed in intact males. c-FOS expression is a marker of neuroplastic change occurring within CNS neurons that have been activated after a noxious peripheral event.

Progesterone has also been demonstrated to influence pain behavior in rats. In one study, injection of complete Freund's adjuvant, an inflammatory agent, was given to four groups of rats: (1) those with normal estrus cycles, (2) those that were lactating (high progesterone levels), (3) ovariectomized (OVX) rats given progesterone supplementation, and (4) ovariectomized (OVX) rats given normal saline. Paw withdrawal latency to painful stimulation of the inflamed paw was measured in each group. Lactating rats and OVX rats that received progesterone supplementation had significantly longer paw withdrawal latencies than normally cycling rats or those that received normal saline. These findings were associated with less dorsal horn c-FOS expression in lactating rats, as well as significantly less pain behavior in the

lactating rats when they were administered an NMDA receptor agonist [26]. Therefore, progesterone appeared to be protective in terms of pain responses in rats, and this action was mediated through lower NMDA receptor activation. The NMDA receptor is an excitatory amino acid receptor that, when activated in the dorsal horn, creates sustained activity within the neuron with resultant long-term potentiation. This receptor is known to play a vital role in the formation of chronic pain through central sensitization.

There is now evidence available in humans as well via advanced imaging studies that demonstrate interactions between estrogen and the mu-opioid receptor system. Using PET scan technology, eight women were studied first during the early follicular phase of their menstrual cycle, when estrogen and progesterone levels are low, and then after receiving high-dose transdermal estrogen supplementation [27]. Eight men were used as a control group. Each group was examined with PET scan under normal (non-painful) conditions and then during a pain challenge (infusion of hypertonic saline into the masseter muscle). During the non-painful state, estradiol increased mu-opioid receptor binding potential in the thalamus, nucleus accumbens, and amygdala. Under painful conditions, there was evidence of increased activation of the endogenous mu-opioid system in the setting of high estradiol that was equivalent to the levels observed in the male controls. While in the setting of low estradiol, there was less activation of this receptor system than in the men. This activation also correlated with the sensory and affective ratings of pain during the test.

When it comes to sex hormones and pain, conflicting evidence appears to exist. For example, as shown above, estrogen activates the endogenous mu-opioid system under certain painful conditions and correlates in this setting with lower pain scores. In addition, menstrual migraine attacks are known to occur in the setting of low or rapidly falling estrogen levels [28]. This data appears at odds with the apparent pronociceptive qualities of estrogen demonstrated in basic science research. There are several potential explanations for this. Estrogen receptors are located throughout the nervous system in areas known to be important in pain transmission. For example, estrogen receptors have been identified on the trigeminal ganglion in the brainstem of both female and male rats with greater density seen in females [29, 30]. Estrogen receptors are also expressed in the dorsal root ganglia of the rat lumbosacral spine [31], as well as in brain areas known to play a role in anxiety and pain such as the hypothalamus, amygdala, and periaqueductal gray (PAG) [32]. Estradiol administration has been shown to differentially regulate neuropeptide expression in these areas [33–35]. Therefore, one explanation of the apparently divergent actions of estrogen on pain is that estrogen may exert different effects depending on its location of action in the nervous system.

Estrogen is also known, however, to exert a simultaneous twofold activity on neurons: both gene-regulated nuclear transcriptional effects and immediate non-gene-regulated membrane excitability effects. For example, high estrogen levels result in increased expression of the inhibitory neurotransmitters NPY and galanin in rat trigeminal ganglion, while CGRP expression remains stable across the estrus cycle [30]. Yet exposure to estrogen activates extracellular-signaling protein kinase

(ERK-1) in cultured trigeminal ganglionic neurons [36]. Activation of ERK-1 in dorsal horn neurons facilitates activity and contributes to the development of central sensitization in these neurons [17]. These apparently opposing effects of estrogen have been proposed to explain the phenomenon of menstrual migraine [36], but may also extend to other chronic pain disorders. Estrogen, for example, may both act to modulate pain through its action on endogenous opioid systems while also predisposing neurons toward sensitization [37]. This could explain potentially different effects of estrogen on different types of pain (i.e., acute vs. sustained), which has clear clinical importance, but also has relevance for the type of experimental pain stimulus that is applied in the laboratory setting.

These seemingly disparate roles for estrogen should not be surprising. Opioid analgesics themselves are known to act in such a manner. Although opioids clearly decrease pain transmission by their potent actions at mu-opioid receptors, they are also capable of producing hyperalgesia and increasing sensitization, a phenomenon referred to as opioid-induced hyperalgesia (OIH) [38]. Although the underlying mechanisms of OIH remain under investigation, a strong role for NMDA receptor mechanisms has been implicated [39]. Since the NMDA receptor is a potential site of action of sex hormones, this may have clinical relevance in terms of sex differences in response to opioid analgesics (discussed later on in this chapter). There is some limited evidence in rats for sex differences in opioid-induced hyperalgesia. Female rats have been shown to develop significantly greater hyperalgesia in response to low (subanalgesic) doses of morphine as compared to male rats [40]. These effects were attenuated by the NMDA receptor antagonist ketamine. Therefore, similar to opioid agonists, estrogen itself may exert divergent actions on the CNS (pro- vs. antinociceptive) dependent on dosing and/or timing of administration and perhaps other as yet unidentified parameters.

Exogenous Hormones and Pain

In addition, other estrogen-like compounds, both those synthesized for contraceptive and hormone therapy purposes and those found in the environment as contaminants (xenoestrogens), are capable of binding to estrogen receptors and exerting actions on the central nervous system (CNS). There is some limited evidence that pharmacological use of hormone therapy may result in changes in pain sensitivity. One study comparing experimental pain responses in postmenopausal women on and off hormone therapy (HT) to responses in men found significantly lower heat pain threshold and tolerance in women on HT as compared to women not on HT and men [41]. Several cross-sectional studies in this arena have also shown increased frequency and/or severity of several pain conditions in postmenopausal hormone therapy users as compared to nonusers, including temporomandibular joint disorder, orofacial pain, and low back pain (LBP) [42–44]. It is, however, not possible to draw cause and effect conclusions from these studies due to their cohort design.

The studies involving oral contraceptive (OC) use and pain show varied conclusions, with some showing no difference in pain sensitivity between users and nonusers, some demonstrating less pain sensitivity in OC users, and still others show increased pain sensitivity in OC users [42, 45–47]. There are several likely reasons for this phenomenon, including the cross-sectional design of such studies, relatively short follow-up times, wide variability in the specific hormonal formulations used, different durations of use of OC by subjects being tested, and different durations (acute vs. chronic) and types of pain conditions (visceral, somatic, neuropathic) being examined. Recently, an effect of oral contraceptives on the phenomenon of diffuse noxious inhibitory control (DNIC) has been suggested [48]. DNIC involves the inhibition of second-order neurons in the dorsal horn in response to an applied nociceptive stimulus [49]. This can be taken as a measure of endogenous pain modulation, disturbances in which are felt to contribute to higher rates of chronic pain conditions in women [50]. Mechanical pressure stimuli were applied to 15 women taking OC and 17 normally menstruating women [48]. Pain levels were assessed before, during, and after immersion of the contralateral hand in ice water, a cold pressor test (CPT) to elicit DINC. For all subjects, the pain induced by the test stimulus decreased during the CPT. However, the decrease in the normally menstruating women was greater than the OC group, suggesting that endogenous pain modulation may be less robust in women using oral contraceptives. It should be noted that even in this study women were taking various oral contraceptive combinations. In addition, although all women in the OC group had been on oral contraceptives for at least 3 months, the total duration of use of each subject was not noted in this study and is likely to have been extremely variable, highlighting the difficulties of studying the effects of OC on pain sensitivity. Therefore, although further research is needed to clarify the effects of oral contraceptives on pain in acute to subacute settings, another area for future clarification is the long-term effects of oral contraceptive use on the pain modulatory system, given that these medications are often taken for relatively long time periods.

In addition, estrogen-like compounds are found plentifully in the environment and may have important health consequences for humans. Much concern about these substances has focused on their effects on reproductive organs and, specifically, male fertility [51]. However, more and more evidence suggests that these xenoestrogens can affect the CNS and influence behaviors such as pain and memory. Several studies have demonstrated cognitive behavioral changes in both animals and humans exposed to common xenoestrogens [52, 53]. There is now evidence that pain behavior is altered in rats exposed to xenoestrogens during the perinatal period. Both female and male offspring of mother rats treated with bisphenol A, a plastic byproduct with estrogen-like activity commonly found in the environment, demonstrated increased pain behavior in response to formalin injection [54]. In another study, female rats that were exposed prenatally to 17-alpha-ethynylestradiol, a synthetic estrogen widely used for oral contraception due to its high affinity for estrogen receptors, or methoxychlor (MXC), a pesticide with home, garden, and livestock applications, showed increased pain behavior after formalin injection [55]. Therefore, risk for certain pain conditions with potential hormonal influences may be increasing over time with increased environmental contamination with estrogen-like compounds, the effects of which are impossible to measure on an individual basis.

Sex Differences in Analgesia

Prior to 1993, the Federal Drug Administration (FDA) excluded women from Phase I and Phase II clinical trials in order to avoid potential risks to childbearing potential [56]. Only over the last two decades, therefore, has recognition of sex differences in response to pharmacological substances been established. Interest in studying sex differences in health conditions and their treatment has burgeoned over this time. Because of the strong sex differences in clinical pain conditions, it seems likely that sex differences may likewise exist in terms of treatment response to both drug and nondrug therapies for pain. Chronic pain is a complex disorder, the treatment of which poses myriad clinical challenges. Improving our understanding of factors affecting response to treatment is, therefore, both necessary and desirable.

Opioid analgesics remain the most potent and effective therapy available for moderate to severe acute pain. However, use of opioids in the clinical setting is hampered by substantial adverse effects such as nausea, vomiting, and sedation, as well as the more concerning risks of respiratory depression and cardiac arrhythmia. There are also concerns of abuse and addiction. The long-term use of opioids for the treatment of chronic nonmalignant pain is even more complicated and controversial. With chronic use, issues of tolerance and hyperalgesia (discussed above) increase in significance. Among the recognized adverse consequences of chronic opioid use is a significant reduction in reproductive function. Opioids are known to decrease circulating gonadal hormones by suppressing their release at the level of the hypothalamus [57]. Men with chronic non-cancer pain have demonstrated significant reduction in serum testosterone levels associated with decreased libido and potency when treated with intrathecal opioids [58, 59]. In women, treatment with intrathecal opioids has been associated with amenorrhea [60]. More recently, women being treated with sustained action oral opioid analgesics administrated either orally or transdermally demonstrated significantly decreased ovarian hormone and adrenal androgen levels and were shown to cease menstruation shortly after initiating sustained opioid therapy [61]. These findings have important clinical implications in terms of reduced fertility and early osteoporosis and also suggest a mechanism for opioid tolerance and hyperalgesia, making hormone therapy a potential adjuvant treatment option. Given the challenges involved in opioid use as well as their strong interactions with gonadal hormone systems, it is not surprising that the majority of attention in terms of sex-based differences in analgesia has focused on opioid analgesics.

Studies in both human and animal models have provided evidence that sex differences in response to opioids do in fact exist. However, establishing a clear or clinically useful pattern has proven difficult. In part, this is likely due to wide variation in study design used to examine these differences, including pain model used, mechanism of administration of medication, and analgesic administrated (i.e., mu, mu/kappa mixed, kappa opioid agonists) [62]. The largest portion of the human literature has focused on studies of postoperative pain using patient-controlled analgesia (PCA) as the vehicle of administration and mu-opioid analgesics as the medications studied. Many of these studies were initially aimed at evaluation of opioid consumption, which was lower in females than in males even when controlled for

body weight [63]. However, since females have generally been shown to experience greater adverse effects from opioids than do men, measurement of consumption alone is insufficient [64].

A recent systematic review of the literature on sex differences in opioid analgesia revealed several important findings which are summarized below [65]. (1) In studies of experimentally induced pain, mu-opioid analgesics demonstrated greater efficacy in women. When morphine alone was examined in an experimental pain setting, the effect size of this difference increased. (2) The data for clinical studies was less clear. Grouping all clinical studies on sex differences in mu-opioid analgesia revealed no significant sex effect. However, limiting the analysis to studies using PCA as mode of administration and morphine as the analgesic examined revealed greater efficacy for morphine in women with an effect size of 0.36. (3) Interestingly, these sex differences did not exist in studies where pain relief was measured over short time periods, suggesting that duration of use is likely to be important. (4) In addition, for mixed mu/kappa opioids, experimental pain studies revealed no significant sex effect, while clinical studies showed a strong sex effect with greater efficacy in women. The authors propose this may be due to the specific pain model studied clinically using mu/kappa opioids, which was postoperative pain after third molar surgery. Further research in this arena using more diverse pain models is recommended.

Investigation of the potential mechanisms behind sex differences in analgesia are ongoing. Some of the variations observed in opioid analgesia may be due to differences in drug pharmacokinetics. In fact, morphine has been shown to have not only a greater efficacy in women but also a slower onset and longer duration of action [64]. Pharmacodynamic variables may also play a role in sex differences in analgesia such as differences in mu-opioid receptor density, affinity of opioids for these receptors, and mu-opioid receptor signal transduction [56]. Furthermore, estrogen has been shown to influence these variables in both animal and human models [66–68]. However, it is likely that observed sex differences in analgesia are due to more than pharmacokinetic and pharmacodynamic differences alone, as sex differences have also been found in nondrug analgesic mechanisms such as stress-induced analgesia. For example, stress-induced analgesia in gonadally intact male but not female mice is NMDA-receptor mediated [69]. In other words, analgesia in males and females may occur not only to different extents in response to the same drug but also by different underlying mechanisms.

In 2007, an International Association for the Study of Pain (IASP) consensus report on sex and gender differences in pain and analgesia determined that, although sex differences in both pain and analgesia clearly exist, there does not appear to be sufficiently strong enough evidence at this time to warrant sex-specific interventions for the treatment of pain [70]. Several important areas for future research were recommended, including further elucidation of the hormonal versus sex chromosome contributions to sex differences in pain and analgesia, how chronicity of pain plays a role in sex differences in pain and analgesia, and to what extent sex differences in pain and analgesia are due to qualitative (i.e., mechanistic) differences in pain modulation.

Musculoskeletal Effects of Estrogen

Thus far, this chapter has focused on the effects of sex hormones on pain responsiveness in the nervous system. This may help to explain the majority of the sex differences that are observed clinically for certain pain disorders such as migraine headache, irritable bowel syndrome, and fibromyalgia. However, sex differences are also observed for certain inflammatory and arthritic disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and osteoarthritis, as well as some less specific types of musculoskeletal pain (e.g., low back and pelvic girdle pains) for which differences in pain threshold and tolerance may be an incomplete explanation.

Estrogens are known to affect the immune system in complex ways, and women are known to demonstrate a more robust inflammatory response [71]. As a result, women are at significantly higher risk of developing autoimmune conditions and many types of inflammatory arthritis than are men. Yet, the effects of estrogen on inflammation are multifaceted and depend on a variety of factors, including the hormone levels and time course of inflammation [71]. In addition, estrogen may affect certain cytokines in opposite manners, which may explain the differing effects of pregnancy on rheumatoid arthritis and SLE [24]. In addition, although implicated to play an etiological role in the preponderance of inflammatory disorders seen in women, estrogen also appears to be protective in terms of joint pain.

Estrogen receptors have been identified on articular chondrocytes in both animal and human models. Similar to its actions in neurons, estrogen has been shown to exert its effects on chondrocytes via both genomic and non-genomic (rapid, membrane-activated) mechanisms, although interestingly these rapid effects have been observed in chondrocytes from females only [72]. There is evidence that estrogen may play a protective role in the development of osteoarthritis. In the Women's Health Initiative (WHI) study, postmenopausal women who had undergone prior hysterectomy and were treated with estrogen had a significantly lower rate of joint replacement surgery than women treated with placebo, and women discontinuing hormone therapy in this study complained of more joint pain and stiffness [24]. In addition, blocking of estrogens with aromatase inhibitors is frequently associated with arthralgias, although the exact mechanism underlying this phenomenon remains unclear [73]. Also, in the WHI, estrogen plus progestin did not appear to have the same beneficial joint effects as estrogen alone, and although estrogen in physiological levels seems to be protective to chondrocytes, the reverse is true when levels are higher than normal.

The sex hormones are also known to affect ligaments throughout the body, but perhaps especially in certain anatomical locations such as the pelvic girdle. Pelvic girdle pain (PGP) disorders frequently present with pain in the sacroiliac (SI) joints or pubic symphysis, often during the pregnant or postpartum time period [74]. Sex hormones are capable of altering collagen synthesis [75]. Much attention has been focused on the role of relaxin in ligamentous laxity of pregnancy. Higher relaxin levels have been found in subjects with peripartum pelvic girdle pain [75]. However, in another study, increased joint laxity was seen during pregnancy and up to 6 weeks

postpartum, but degree of laxity did not correlate with serum relaxin levels [76]. Therefore, it is likely that relaxin levels are an insufficient explanation for peripartum joint laxity and PGP. For example, relaxin has been shown to decrease the synthesis and secretion of interstitial collagen in animal models [77, 78]. High-dose, but not low-dose, relaxin decreased collagen content in the rat pubic symphysis. However, in estrogen-primed rats, low-dose relaxin was sufficient to decrease collagen content to the same degree as high-dose relaxin in non-estrogen-primed animals, indicating a synergistic relationship [79]. Although degree of laxity in the joints of the pelvis has not been shown to correlate with pelvic girdle pain during pregnancy, asymmetrical laxity in the SI joints measured with Doppler imaging does correlate with pelvic girdle pain during pregnancy and the postpartum time period [80]. It seems likely that sex hormones play strong roles in ligamentous laxity and may contribute to a preponderance of musculoskeletal pain and injuries unique to women.

Although much remains to be uncovered regarding the role that estrogen plays in inflammation, joint health, and ligamentous integrity, potential treatment options are under investigation. Two nutritional compounds currently under investigation for their preventative role in joint pain and arthritis are the omega-3 fatty acids found abundantly in fish oil and moderate- to high-dose vitamin D supplementation [81]. Both vitamin D [82] and omega-3 fatty acids [83, 84] have shown some promise in terms of their effects on musculoskeletal pain and joint health. Currently, both are being studied in a large-scale randomized controlled trial funded by the National Institutes of Health [81]. Such treatments are particularly intriguing due to their potential to prevent disabling, chronic pain conditions that, once developed, are often extremely challenging to treat. In addition, specific exercise or neuromuscular training programs that recognize the effects of sex hormones on particularly vulnerable anatomic locations, such as the pelvic girdle and knees, may be another way of preventing musculoskeletal pain and joint injuries in women particularly in certain population subsets such as peripartum (see Chap. 9), postmenopausal (see Chap. 12), and female athlete (see Chap. 10).

Conclusion

Ongoing research into the hormonal, structural, lifecycle, psychological, and sociocultural variables that influence pain will likely lead to more effective treatments and potentially help to prevent chronicity in the case of certain pain conditions. Sex-specific treatments for pain may be in our future. Until that time, a thorough understanding of the pain conditions that most frequently affect women will assist healthcare providers in evaluating and treating their female patients with pain disorders to the best of our current knowledge, as well as helping to prevent the occurrence of common pain problems in women through targeted strategies. The goal of this chapter is to provide clinicians with a clinically useful information source that will elucidate the most common pain disorders in women and understand the full spectrum of available treatment options.

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Chapter 2
The Neuroanatomy of Female Pelvic Pain

Frank H. Willard and Mark D. Schuenke

Introduction

The female pelvis is innervated through primary afferent fibers that course in nerves related to both the somatic and autonomic nervous systems. The somatic pelvis includes the bony pelvis, its ligaments, and its surrounding skeletal muscle of the urogenital and anal triangles, whereas the visceral pelvis includes the endopelvic fascial lining of the levator ani and the organ systems that it surrounds such as the rectum, reproductive organs, and urinary bladder. Uncovering the origin of pelvic pain patterns created by the convergence of these two separate primary afferent fiber systems – somatic and visceral – on common neuronal circuitry in the sacral and thoracolumbar spinal cord can be a very difficult process. Diagnosing these blended somatovisceral pelvic pain patterns in the female is further complicated by the strong descending signals from the cerebrum and brainstem to the dorsal horn neurons that can significantly modulate the perception of pain. These descending systems are themselves significantly influenced by both the physiological (such as hormonal) and psychological (such as emotional) states of the individual further distorting the intensity, quality, and localization of pain from the pelvis.

The interpretation of pelvic pain patterns requires a sound knowledge of the innervation of somatic and visceral pelvic structures coupled with an understanding of the interactions occurring in the dorsal horn of the lower spinal cord as well as in the brainstem and forebrain. This review will examine the somatic and visceral innervation of the major structures and organ systems in and around the female pelvis. It will then consider the properties of visceral afferent fibers, their interactions in the spinal cord, as well as their modulation by descending systems from the brainstem and cerebrum.

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Somatic Structures of the Pelvis

Ligamentous Structure of the Pelvis

The pelvic basin is a funnel-shaped structure bound anteriorly by the pubic symphysis and posteriorly by a complex of ligaments and muscles related to the thoracolumbar fascia [1]. The ligaments of the posterior aspect of the pelvis are closely associated with muscles derived from the back, abdomen, and upper and lower extremities. The anterior ligaments of the pelvis surrounding the pubic symphysis are intimately associated with the abdominal muscles and the adductor muscles of the lower extremity.

Pubic Symphysis

The pubic symphysis is a fibrocartilaginous joint between the bodies of the two pubic bones (Figs. 2.1 and 2.2) [2]. Although the joint is generally considered to be

Fig. 2.1 The pubic symphysis. The *upper photograph* demonstrates an anterior view of the pubic symphysis in an 84-year-old female after removing the skin, subcutaneous fat and fascia, and thigh muscles. The *arrows* indicate the fibrocartilage disc in the joint. The *lower photograph* was taken following removal of the pubic symphysis to reveal the periosteum on the posterior aspect of the pubic rami. The *arrows* indicate where the fibrocartilaginous disc was located

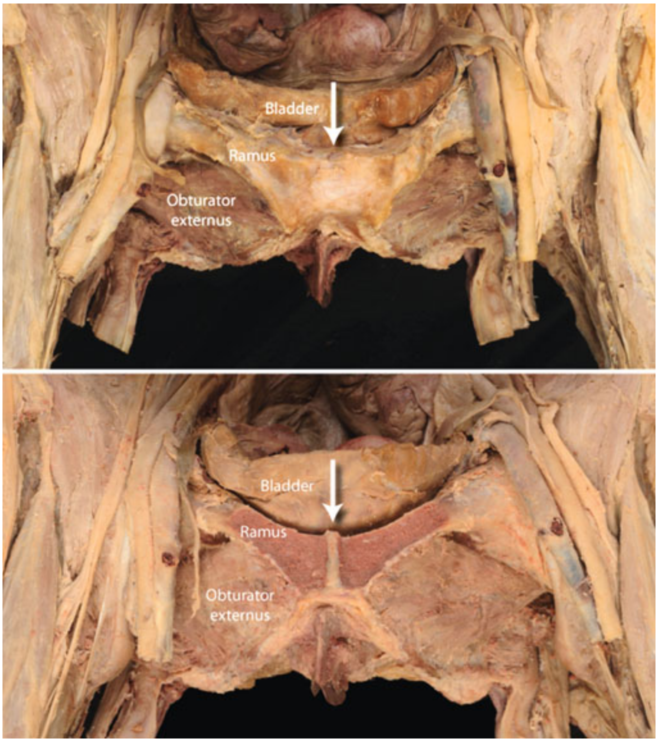

Fig. 2.2 The pubic symphysis. The *upper photograph* demonstrates an anterior view of the pubic symphysis in a 50-year-old female after removing the skin, subcutaneous fat and fascia, and thigh muscles. The *arrow* indicates the fibrocartilage disc in the joint. The *lower photograph* was taken following section of the pubic symphysis in the coronal plane to reveal the fibrocartilaginous located between the two pubic rami

restricted in motion, there is a slight displacement that can occur between the two articular surfaces. This displacement consists of a vertical shift of up to 2 mm and rotation of approximately 1° [3]. For most individuals, the two joint surfaces approximate each other symmetrically. However, a disparity in the heights of the two sides of the joint has been observed and is present mainly in females. The articular surface is covered with a thin layer of hyaline cartilage which appears to decrease with age. The joint is stabilized by superior and inferior ligaments, a multilayered anterior ligament, and a little-studied posterior ligament. Between the two articular surfaces is an interpubic disc composed of fibrocartilage (Fig. 2.3). A retropubic eminence can be present in multiparous females. An interpubic cleft is seen in the normal joint, which has been suggested to represent a possible joint space. However, the pubic symphysis generally is not considered a synovial joint by most accounts.

Muscle attachments surrounding the joint include the rectus abdominis superiorly and the adductor longus inferiorly, while an aponeurosis extends across the pubic symphysis to connect these two muscles. Rotational and extensional injuries

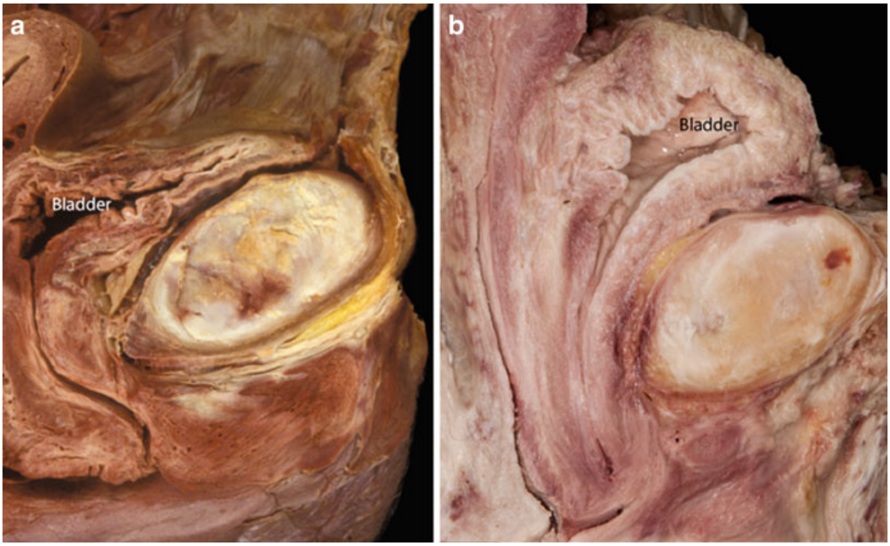

Fig. 2.3 The pubic symphysis. (**a**) A sagittal view of the pubic symphysis in a 54-year-old female. (**b**) A sagittal view of the pubic symphysis in an 84-year-old female. Both views reveal a dense connective tissue capsule surrounding the joint and a degree of fibrocartilage degeneration (discolored material) in the center of the joint. The bladder in (**a**) is relatively normal in size while the bladder wall in (**b**) is hypertrophied

can stress this aponeurosis resulting in radiographically demonstrable dysfunction about the joint [4]. A pubalgia, or sports hernia, has been demonstrated on MR imaging to involve damage to the attachments of one or both of these two muscles or to the joint itself, a condition termed osteitis pubis [4–6]. Suggested innervations of the pubic symphysis include the pudendal nerve, genitofemoral nerve, and iliohypogastric and ilioinguinal nerves [2].

SI Joint Capsule and Associated Ligaments

The sacroiliac joint capsule has a smooth anterior surface (Figs. 2.4 and 2.5) and an irregular, woven posterior surface (Fig. 2.5) [1, 7]. The anterior surface of the joint capsule is in contact with the piriformis muscle and lumbosacral plexus. The superior aspect of the capsule blends with the iliolumbar ligament, while the inferior aspect blends with the sacrospinous ligament anteriorly and the sacrotuberous ligament posteriorly. Bands of the iliolumbar ligament form tight hoods arching over the L4 and L5 ventral rami (Fig. 2.4) and are potentially a source of compression neuropathy [8].

Posterior muscles influencing the sacroiliac joint include the multifidus muscle on the midline and its fusion to the gluteus maximus through a connective tissue raphe [9] and the biceps femoris across the sacrotuberous ligament [10]. In addition,

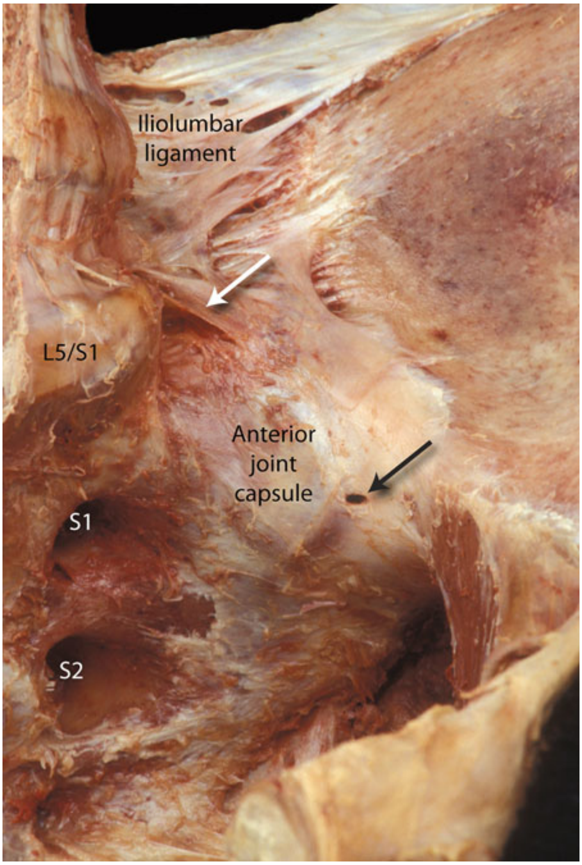

Fig. 2.4 The anterior ligaments of the sacroiliac joint in a 54-year-old female. This is an anterior view into the pelvis following the removal of all organs and neurovascular structures. The iliolumbar ligament is seen blending into the superior portion of the anterior sacroiliac joint capsule. The *white arrow* indicates a ligament forming a hood that covered the L5 ventral ramus. The *black arrow* indicates a defect in the joint capsule. This defect formed an open conduit into the joint. If anesthetic had been injected into the joint capsule, it would have leaked out through this defect. The defect was positioned deep to the lumbosacral trunk (L4–L5) in the endopelvic fascia

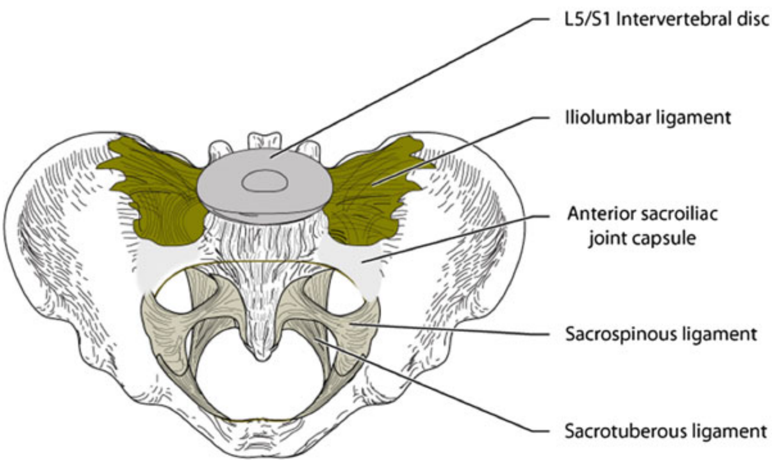

Fig. 2.5 The anterior ligaments of the sacroiliac joint. This drawing illustrates the position of the iliolumbar ligament superior to the sacroiliac joint capsule and the sacrospinous ligament inferior to the joint capsule. The sacrotuberous ligament is located posterior to the joint capsule

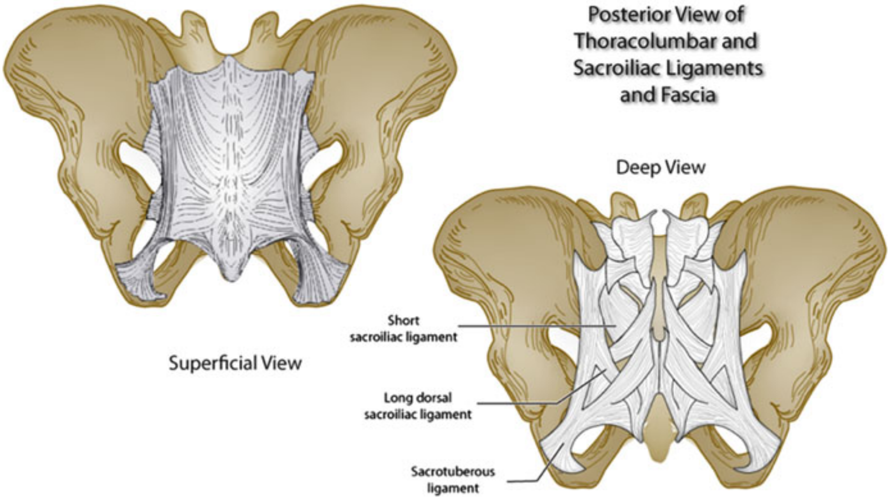

Fig. 2.6 The posterior ligaments of the sacroiliac joint. The drawing on the *left* illustrates the combined aponeuroses of the latissimus dorsi, posterior inferior serratus, and erector spinae muscles covering the multifidus muscle on the posterior aspect of the sacrum. The drawing on the right illustrates the short sacroiliac ligaments following the complete removal of the multifidus muscle. The short sacroiliac ligaments and the multifidus muscle lie in a trough or gutter formed by the medial sacral tubercles on the midline and the lateral sacral tubercles along the lateral border of the sacrum. Deep to the short sacroiliac ligaments are the dorsal sacral foramina and their dorsal sacral primary rami

the piriformis is positioned laterally on the sacrum. The latissimus dorsi through its attachment to the thoracolumbar fascia and the aponeurosis of the erector spinae muscles has also been postulated to influence the sacroiliac joint [10–12].

The posterior aspect of the sacroiliac joint is protected by the interosseous ligaments located in the narrow space or joint cleft between the sacrum and the ilium, as well as the long and short sacroiliac ligaments located on the external surface of the joint between the posterior superior iliac spine (PSIS) and the spinous processes of the sacrum (Figs. 2.6 and 2.7). The posterior portion of the joint capsule is woven into the superior and medial bands of the sacrotuberous ligament. The posterior aspect of the joint capsule is innervated by the small branches from the dorsal primary rami of L5, S1, and S2 [13, 14]. A description of small twigs from the ventral primary rami of the lumbosacral plexus has been published in abstract form but awaits further study [15]. The sacrotuberous ligament extends from the ischial tuberosity to the coccyx, sacrum, and ilium (Figs. 2.6 and 2.8). This ligament is arranged in a three-layered sandwich with several taut internal ligamentous bands that are covered with outer and inner layers of investing fascia derived from the sacroiliac joint. The outermost layer of the sacrotuberous ligament extends onto the conjoined portion of the thoracolumbar fascia composed of aponeurosis of the latissimus dorsi

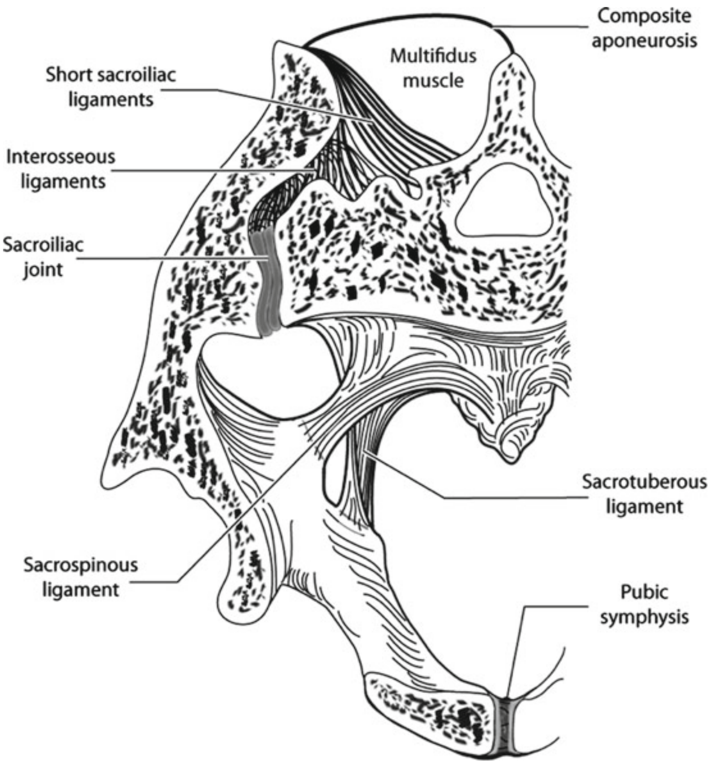

Fig. 2.7 An axial plane section through the sacroiliac joint. The sacroiliac joint is seen as two opposed cartilaginous surfaces between the ala of the sacrum and the internal surface of the ilium. The joint is located anteriorly. Posteriorly, the gap between the sacrum and ilium is filled with irregular bands of dense connective tissue termed the interosseous ligaments. Further posterior, the bed of the multifidus is composed of short sacroiliac ligaments (Figure modified from [1])

and the aponeurosis of the erector spinae muscles. The sacrotuberous ligament has been demonstrated to contain terminal ramifications, some appearing similar to naked nerve endings, while others resembling Ruffini endings [16].

At the superior margin of the SI joint capsule lies the iliolumbar ligament (Figs. 2.4 and 2.5). This ligament arises medially from the transverse process of the fifth, and in some cases fourth, lumbar vertebra and attaches laterally to the crest of the ilium as well as blends into the SI joint capsule [7]. In general, the ligament is composed of two broad anterior and posterior bands; however, complex interweaving can also occur throughout the ligament. Strains involving the ligament are described as iliolumbar syndrome and can involve a pain similar to sciatica [17]. This pain may arise from the internal innervations of the ligament or from the ligament's close relationship with the ventral rami of L4 and L5 [8].

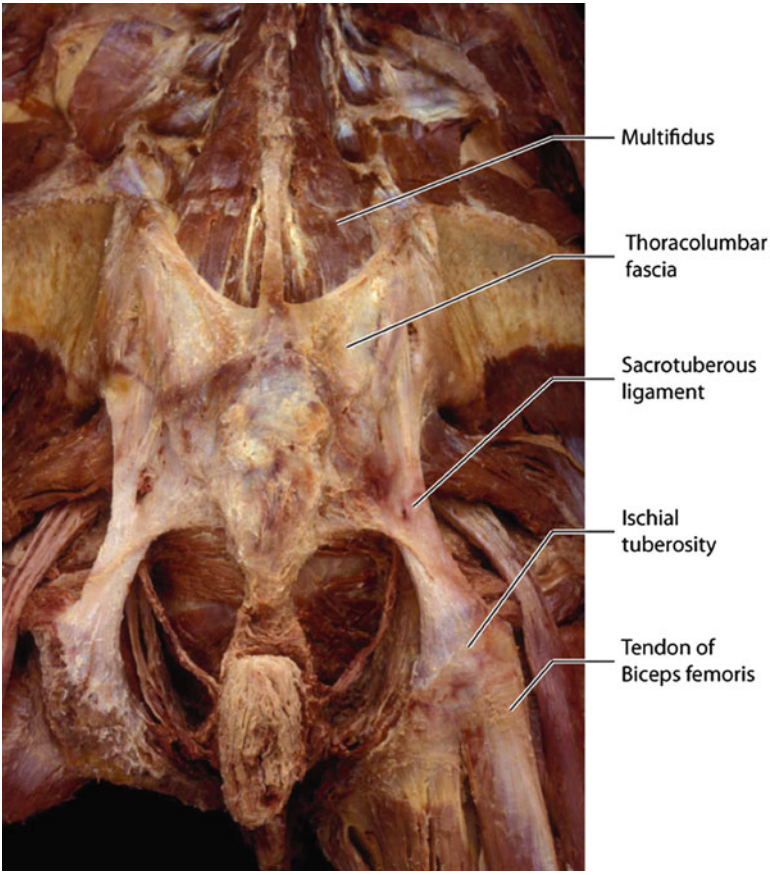

Fig. 2.8 The posterior ligaments of the sacrum. This is a posterior view of the sacrum after removing the gluteus maximus and medius as well as the iliocostalis and longissimus muscles. The multifidus muscle is seen entering a dense connective tissue covering composed of the combined aponeuroses of the latissimus dorsi, posterior inferior serratus, and erector spinae muscles. This composite structure (also termed posterior layer of the thoracolumbar fascia) is continuous with the sacrotuberous ligament and the tendon of the biceps femoris (as seen on the right side only in this illustration). Inferior and medial to the sacrotuberous ligament, the ischiorectal (ischioanal) fossa has been opened and the levator ani and external rectal sphincter muscles exposed

Somatic Nerves Associated with the Pelvis

The Lumbar Plexus: Anterior Cutaneous Innervation in the Pelvic Region

The abdomen is banded by six thoracic spinal nerves that form dermatomes arranged in a superioposterior to inferoanterior orientation (Fig. 2.9) [1, 18]. Five of these nerves are termed thoracoabdominal (T7–T11) since they begin in the thorax and

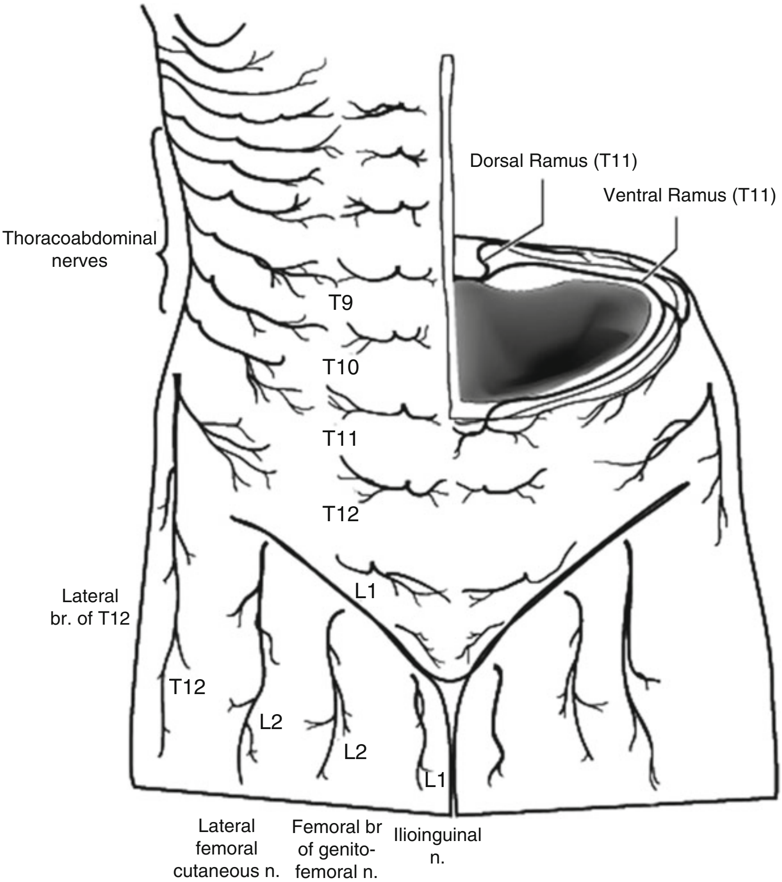

Fig. 2.9 The anterior peripheral nerves of the lower abdomen, pelvis, and thigh. The *lower* five thoracic spinal nerves, termed thoracoabdominal nerves, form bands circumscribing the torso. The first lumbar spinal nerve also follows this pattern, forming the iliohypogastric and ilioinguinal nerves. The terminal branches of the ilioinguinal nerve reach the anterior portion of the vulva and the medial aspect of the thigh (L1). The femoral branch of the genitofemoral nerve and the lateral femoral cutaneous nerve form medial and lateral bands, respectively, containing L2 on the anterior thigh. Finally, a lateral branch from the subcostal nerve brings T12 downward onto the lateral thigh (Figure modified from [95])

terminate in the abdomen. The sixth dermatome is the subcostal nerve (T12). Below the subcostal nerve is an additional dermatome band created by the iliohypogastric and ilioinguinal nerves (L1); twigs from the ilioinguinal nerve extend downward onto the anteromedial thigh as well as into the groin region. Distal twigs from the iliohypogastric nerve reach the mons pubis, while those from the ilioinguinal nerve provide cutaneous innervations to the anterior portions of the vestibule and labia. Spinal root L2 also contributes to the lateral femoral cutaneous nerve and the genitofemoral nerve

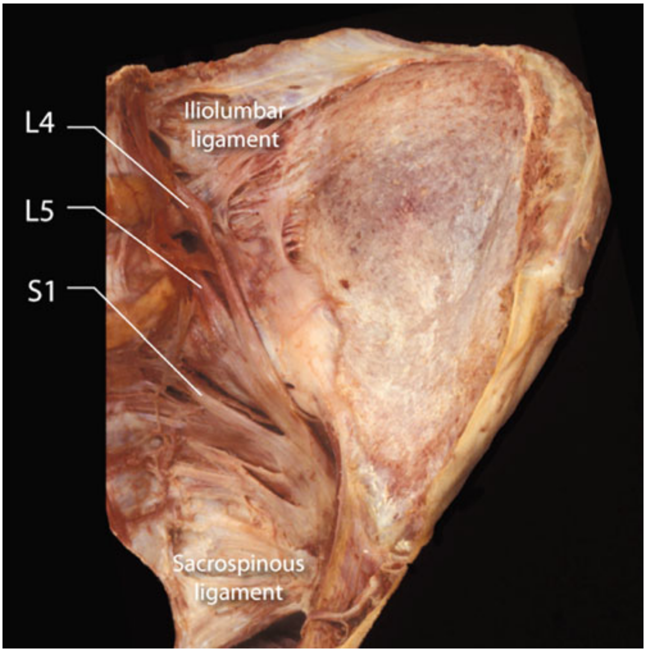

Fig. 2.10 The lumbosacral plexus. This is an anterior view of the lumbosacral plexus in a 54-year-old female. The organ system and surrounding visceral fascia have been removed from the pelvic basin. The lumbosacral trunk (L4 and L5) can be seen passing out from under bands of the iliolumbar ligament and joining the sacral ventral rami to form the sacral plexus. This plexus exits the pelvic basin by passing through the greater sciatic foramen

as well as the femoral nerve and the obturator nerve. Four cutaneous nerves – the lateral branches of T12, the lateral femoral cutaneous nerve, the femoral branches of the genitofemoral nerve, and the terminal branches of the ilioinguinal nerve – form successive dermatome bands from lateral to medial across the thigh (Fig. 2.9). These dermatomes are of special interest since much visceral nociceptive sensory information arrives in the T12–L2 spinal cord segments via the white rami at these levels (as described below). As such, this visceral input is commonly referred to the somatic body innervated by these segments and presents as body wall pain following the iliac crest, the groin region, and the thigh.

The Lumbosacral Plexus: Posterior Cutaneous Innervation in the Pelvic Region

The final two ventral rami of the lumbar nerves (L4 and L5) join together to form the lumbosacral trunk (Fig. 2.10). This combined nerve enters the pelvic basin by passing over the ala of the sacrum in close juxtaposition with the lateral margin of the L5/S1 disc. Once in the pelvic region, the lumbosacral trunk joins with the

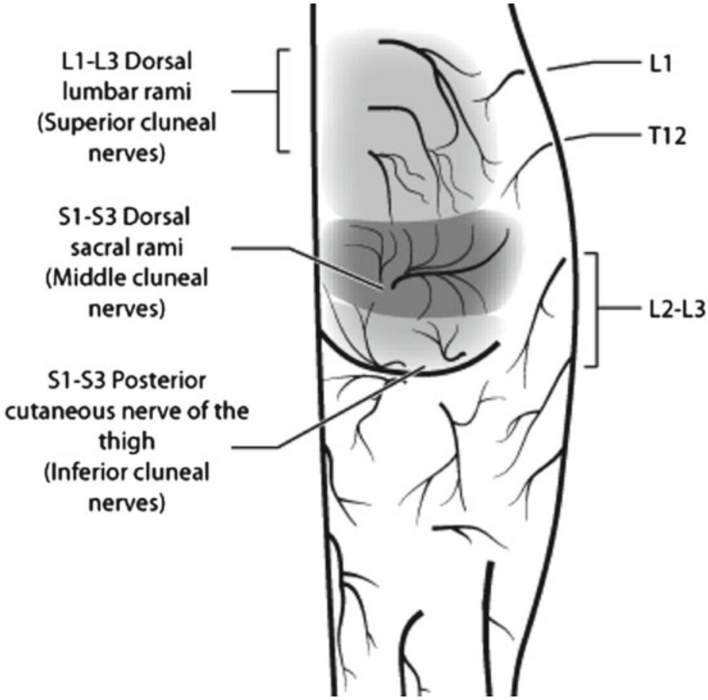

Fig. 2.11 The posterior peripheral nerves of the lower abdomen, pelvis, and thigh. Lateral branches of the upper three lumbar dorsal primary rami cover the posterior lumbar region forming the superior cluneal nerves; L4 and L5 typically lack lateral cutaneous branches. The dorsal primary rami of the sacral region (S1–S3) provide the middle cluneal nerves. Note that a contribution to the dorsal sacral rami has been noted from the L5 dorsal ramus as well. Finally, the ventral primary rami (S1–S3) provide the posterior cutaneous nerves of the thigh that curl around the gluteal fold to reach the territory of the middle cluneal nerves (figure modified from reference [18])

ventral rami of S1 through S3. These five roots give rise to the superior and inferior gluteal nerves and the sciatic nerve as well as the pudendal nerve and the nerves to the external rotators of the thigh such as the obturator internus. For the most part, the superior (L4, L5, and S1) and inferior (L5, S1, and S2) gluteal nerves are motor nerves; however, a few scattered branches continue through the muscle to reach the skin over the posterior buttocks (mostly from the S2 level). The posterior femoral cutaneous nerve receives contributions from ventral rami S2 and S3. This nerve also gives rise to the inferior cluneal nerves (or gluteal branches) to the inferior margin of the gluteal fold and twigs to the posterolateral perineal region (perineal branches) before extending downward along the posterior aspect of the thigh. The inferior cluneal nerves are three or four in number and curve upward from the gluteal fold to cover the inferior skin over the gluteal muscles (Fig. 2.11). Note that the skin over the gluteal muscles also receives cutaneous innervation from the first and second sacral dorsal primary rami as will be described below.

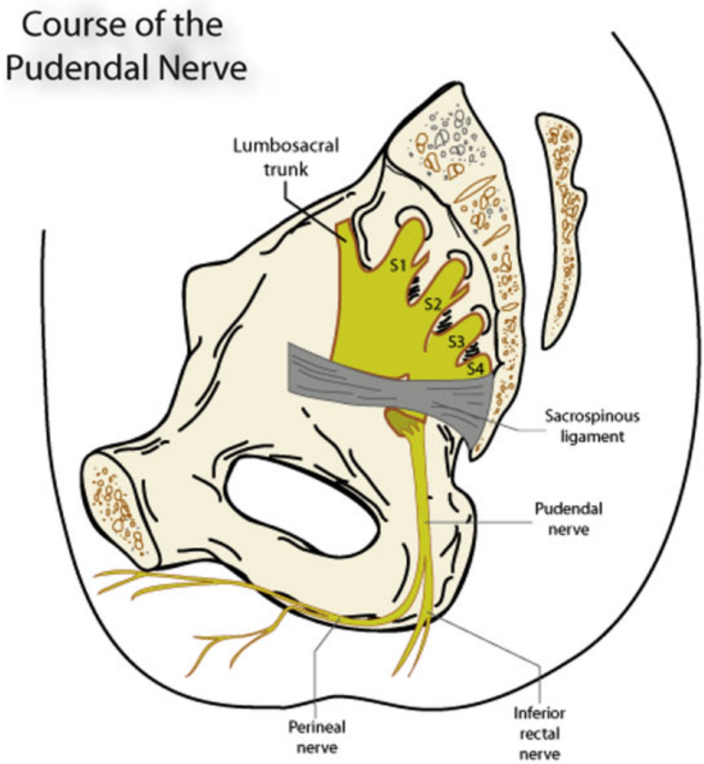

Fig. 2.12 The course of the pudendal nerve. This is a medial view of a sagittal section through the female pelvis to illustrate the course of the pudendal nerve (S2–S4) as it passes around the sacrospinous ligament, attaches to the medial aspect of the ischial tuberosity (pudendal canal), and terminates by passing through the urogenital diaphragm to reach the external genitalia

The pudendal nerve receives contributions from the ventral rami of S2–S4. It passes out of the pelvic basin through the greater sciatic foramen and immediately returns into the pelvis through the lesser sciatic foramen, following which it enters a narrow fascial (pudendal or Alcock's) canal on the inner aspect of the ischial tuberosity (Fig. 2.12). Terminal branches of the pudendal nerve reach the skin in the vestibule and over the posterior labia. It has been suggested that burning pain in the territory approximating the pudendal nerve could represent a form of neuralgia [19]. Although the etiology of pudendal neuralgia is not certain, it has been suggested that entrapment of the pudendal nerve in the fascial canal along the medial aspect of the ischial tuberosity is a strong possibility [20]. At least four entrapment sites have been described for the pudendal nerve: around the piriformis muscle/greater sciatic notch, at the ischial spine, in the pudendal canal on the side of the obturator muscle, and in the distal branches of the nerve [21].

The Lumbar and Sacral Dorsal Primary Rami: Posterior Cutaneous Innervation in the Pelvic Region

Each spinal nerve divides as it leaves the intervertebral foramen to form a ventral and dorsal primary ramus (Fig. 2.9) [1, 18]. The ventral ramus innervates structures that develop ventral to the transverse process of the vertebrae, while the dorsal ramus innervates those structures derived from tissue located dorsal to the transverse process. The ventral rami also innervate the upper and lower extremities. The innervation of the posterior aspect of the pelvis is complex, involving branches from both dorsal and ventral rami.

This posterior region shows the greatest variability of any region in the body when comparing the published dermatome and peripheral nerve maps. At all levels of the spine except C1 and C2 and possibly S3 and S4, the dorsal rami typically divide into medial and lateral branches shortly after their separation from the ventral rami [22]. One of these two branches will provide cutaneous innervation to a vertical band of skin extending from the vertex of the head to the anus and approximately as wide as a vertical line drawn down the back along the medial border of the scapulae. At most levels, this vertical band of skin is partitioned into horizontal segmentally oriented dermatomes by each of the dorsal rami. In the cervical and upper thoracic regions, the cutaneous innervation is provided by the medial branch of the dorsal ramus. However at T6, the cutaneous innervation shifts to the lateral branches of the dorsal rami.

In the lumbar region, L1–L3 dorsal primary rami typically have cutaneous branches that begin at spinous processes as a horizontal orientation but rapidly curve inferiorly to extend downward onto the buttocks to end as the superior cluneal nerves (Fig. 2.11). This downward movement extends the coverage of L1–L3 to make up for the lack of cutaneous branches from L4 and L5. The sacral dorsal rami emerge from their dorsal foramina, divide into medial and lateral branches, and course in the short sacroiliac ligaments deep to the multifidus muscle. Passing through and around the ligaments, the medial branches enter the multifidus, while the lateral branches of S1–S3 join with a contribution from L5 to form a complex arcade that ultimately passes under the long sacroiliac ligament to enter the sacrotuberous ligament [14, 23]. These cutaneous sacral branches then exit the posterior side of the ligament through small defects and pass outward through the gluteus maximus to gain access to the skin over the medal aspect of the buttocks, terminating as the middle cluneal nerves (Fig. 2.11). Irritation of these cutaneous nerves as they pass through the long posterior sacroiliac ligament may play a role in generating diffuse pain over the middle sacral region of the buttocks (J. Carreiro, personal observations). Small twigs from L5 through S2 can be found leaving the dorsal sacral plexus and entering the sacroiliac joint [13, 14]. Sacroiliac joint pain due to irritation of these nerves is estimated to affect 15–25% of patients with axial low back pain [24]. Finally, the lateral branches of S3 and below contribute to a delicate nerve plexus that extends inferiorly to surround the coccyx; this plexus is relatively unstudied but may play a role in coccygodynia (personal observations).

Visceral Nerves Associated with the Pelvis

Distinction Between Pain of Somatic and Visceral Origin

Based on the neuroanatomy of the visceral sensory system, six properties can be derived that help distinguish visceral pain from somatic pain [25, 26]:

1. Visceral pain is not evoked from all viscera; typically solid organs are only innervated in their capsule.
2. Visceral pain is not always linked to visceral organ injury.
3. When evoked, it is diffuse and poorly localized.
4. It is typically referred and not felt at the source.
5. It is produced by stimuli different from those adequate for activation of somatic nociceptors.
6. It is associated with strong motor, emotional, and autonomic responses.

In the following sections, the basis for these distinctions will be considered.

Each organ system in the pelvis is innervated by a dual set of fibers: sympathetic and parasympathetic. These nerves arise from the sympathetic trunk and the sacral spinal nerves, respectively, and form a massive abdominopelvic plexus extending from the thoracoabdominal diaphragm superiorly to the pelvic diaphragm inferiorly. This plexus and its associated connections were initially described as part of the autonomic nervous system by James Langley [27]. Although it was known that the plexus contained sensory fibers as well as efferent fibers, only the efferent fibers were included in the term autonomic nervous system. Since that time, it has become clear that each visceral nerve is mixed having an autonomic (efferent) component that extends outward from the spinal cord or brainstem to the organ system and a sensory (afferent) component that brings information back to the spinal cord or brainstem. The sensory fibers that course along with the sympathetic and parasympathetic fibers are termed visceral afferent (or sensory) fibers [28] and generally are not referred to as “sympathetic afferent” or “parasympathetic afferent” fibers.

Visceral afferent fibers that reach the dorsal horn of the spinal cord, regardless of the route traveled in the body, typically can evoke the sensation of pain. Pain patterns created by visceral afferent fibers are usually diffuse in nature and often are referred to a portion of the somatic body wall. Generally, a given organ will refer pain to a specific set of body somites related to the ontology of the organ system [29] and are referred to as a viscerotome [30]; however, this pattern can be altered if previous pain patterns have been experienced by the individual [31]. An understanding of the pattern of sympathetic and parasympathetic innervation in the pelvis is critical to the diagnosis of pelvic pain since the visceral afferent fibers tend to use the autonomic nerves as their route for gaining access to the spinal cord.

Fig. 2.13 The sympathetic trunk. This is a lateral view of the sympathetic trunk in a 74-year-old female. The three cervical ganglia are seen positioned on the longus cervicis muscles. The thoracic ganglia are seen attached to the intercostal nerves by rami communicantes. The distal thoracic ganglia give off splanchnic nerves that pass through the diaphragm to enter the abdominal cavity and innervate the celiac and superior mesenteric ganglia. Finally, the lumbar trunk is seen passing over the psoas muscle

The Sympathetic Trunk and the Lumbar and Sacral Splanchnic Nerves

The Sympathetic Trunk Extends from the Cranial Base to the Pelvic Basin

The sympathetic trunk begins in the cervical region where it lies on the longus cervicis (colli) muscles (Fig. 2.13). As the trunk enters the thorax, it shifts to a position located adjacent to the heads of the ribs. Under the diaphragm in the lumbar region, the trunk moves medially to pass in an arch around the attachment of the psoas muscle on the anterior longitudinal ligament. At the inferior border of the psoas attachment to the anterior longitudinal ligament, the trunk enters the pelvic basin by passing lateral to the sacral promontory and then coursing along the ventral aspect of the sacrum, positioned just medial to the ventral sacral foramina. Deep in the pelvic basin and directly over the coccygeal segments, the left and right sympathetic trunks unite at the ganglion impar reviewed in reference [1, 18, 32].

The Sympathetic Trunk Is Connected to the Spinal Nerves via Rami Communicantes

Each ganglion has a gray communicating ramus that passes between the adjacent spinal nerve and the trunk (Fig. 2.14). The gray rami are a conduit for efferent fibers arising from neurons in the ganglion to reach the spinal nerve. Once intercalated

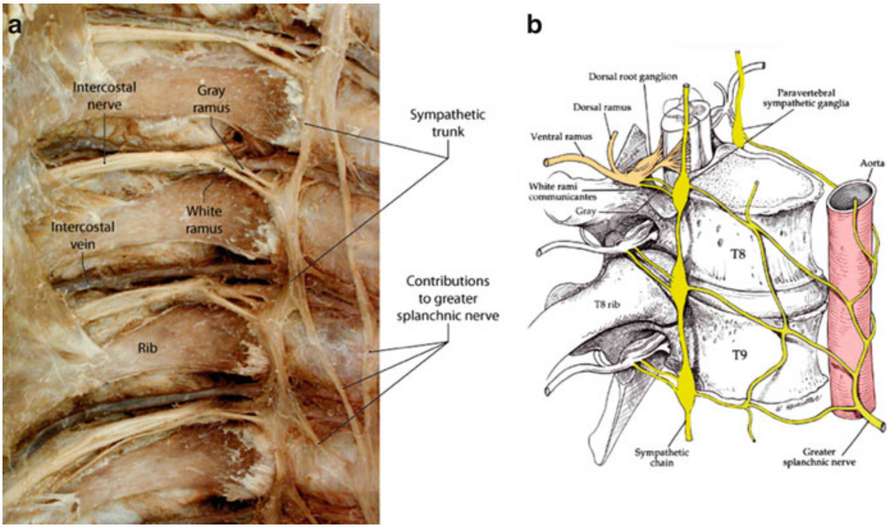

Fig. 2.14 The sympathetic trunk. (**a**) This is an anterior-oblique view of a dissection of the thoracic sympathetic trunk illustrating the white and gray rami. Figure (**b**) is a drawing of the thoracic spine demonstrating the relationship between the spinal nerve, sympathetic trunk, and splanchnic nerves. The spinal nerve is located posterior to the body of the vertebra, the sympathetic trunk is lateral to the body, and the splanchnic nerves progress anterior to the body ((**b**) is modified from [96])

into the spinal nerve, these efferent fibers are carried peripherally to eventually reach their target organs such as smooth muscle of blood vessels and hair follicles as well as the secretory cells in sweat glands. Since all spinal nerves need both vasomotor and secretomotor fibers, there are gray rami at all spinal nerve levels.

Conversely, white rami also pass from the spinal nerve to the sympathetic trunk (Fig. 2.14). These laterally positioned rami act as a passageway for preganglionic axons arising from neurons in the lateral horn of the spinal cord and terminating in either the sympathetic trunk or in a prevertebral ganglion such as the celiac, superior and inferior mesenteric, or hypogastric ganglia. Considering this relationship from the prospective of an individual neuron, a preganglonic motoneuron in the lateral horn of the spinal cord extends its axon through the ventral root to join the spinal nerve and course out of the intervertebral foramen. From the spinal nerve, the axon enters the white ramus to reach the sympathetic trunk. At the point of entry into the trunk, the axon has three options: (1) innervate ganglionic neurons at the level of entry, (2) ascend or descend several levels in the trunk to innervate ganglionic neurons, or (3) leave the trunk by entering a splanchnic nerve and eventually reach a neuron located in a prevertebral ganglion reviewed in reference [1, 18, 32].

The Ganglia in the Sympathetic Trunk Vary Considerably in Size and Function

The trunk has approximately one ganglion for each segment in the thoracic and lumbar regions but only two to three ganglia in the cervical region (Fig. 2.13) and a variable number in the sacral region. The ganglia above T5 tend to be large since they contain the cell bodies for neurons innervating the somatic territories (blood vessels, hair follicles, and sweat glands) and the cell bodies of those neurons innervating the upper thoracic viscera (heart and airways). Below T5, the cell bodies of neurons innervating the abdominal and pelvic viscera have migrated beyond the sympathetic trunk to reach a position surrounding the abdominal aorta. Here, these visceral ganglionic neurons cluster together to form the prevertebral or preaortic ganglia (celiac, superior mesenteric, inferior mesenteric, and hypogastric ganglia).

Communication between the sympathetic trunk and the abdominopelvic prevertebral ganglia occurs through a series of splanchnic (visceral) nerves. The thoracic sympathetic trunk also gives off a series of anteromedially directed thoracic splanchnic nerves (Fig. 2.14) that penetrate the diaphragm to enter the abdomen and reach the celiac and superior mesenteric ganglia. Contributions from thoracic ganglia T5–T9 join together to form the greater thoracic splanchnic nerve; it pierces the crus of the diaphragm and reaches the celiac and superior mesenteric ganglia. Additional small thoracic splanchnic nerves arise from T10 through T12 (often termed lesser and least thoracic splanchnics), but these nerves are inconsistent in nature. Below the diaphragm, the lumbar and sacral portions of the sympathetic trunk also contribute fibers to the abdominopelvic plexus (Fig. 2.15); these contributions are termed lumbar and sacral splanchnic nerves, respectively. As with the thoracic splanchnic nerves, the efferent fibers in the lumbar and sacral splanchnic nerves are preganglionic and terminate by synapsing on a ganglionic neuron located in the prevertebral ganglia such as the superior mesenteric, inferior mesenteric, or hypogastric ganglia. In the female, the hypogastric ganglia are clustered in the endopelvic fascia lying on the transverse cervical ligament and covered by the anterior and posterior sheets of the broad ligament reviewed in reference [1, 18, 32].

Two Routes for Sympathetic Fibers Entering the Pelvis

The sympathetic system for the pelvis has its origin at the thoracolumbar junction involving the lateral horn of spinal cord segments T12–L2. Notably, the ovaries receive sympathetic input from a slightly higher level, around T10–T12, due to their origin from the urogenital ridge. From T12 to L2 levels, fibers can pass through the lower sympathetic trunk and enter the superior hypogastric plexus via a lumbar splanchnic nerve (Fig. 2.15). Once in the plexus, these fibers can descend over the sacral promontory into the pelvic basin to join the inferior hypogastric plexus, ultimately targeting ganglia in the plexus. After leaving the ganglia, sympathetic fibers gain access to individual organs via small branches coursing with the vasculature.

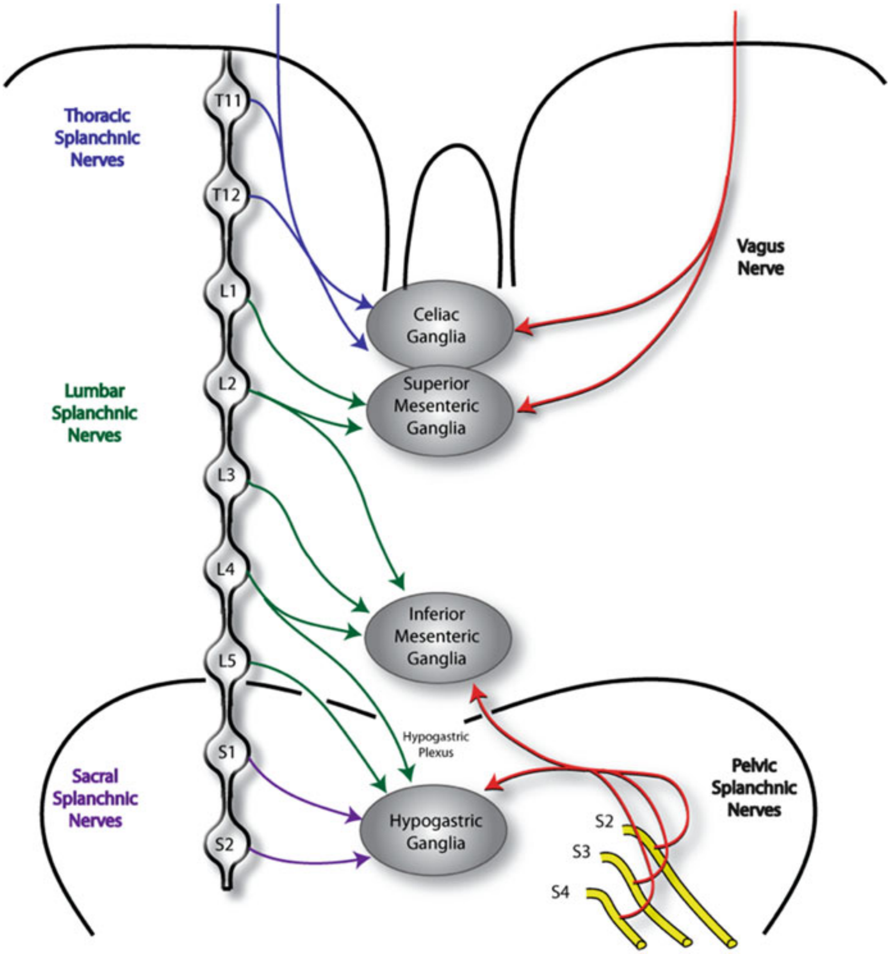

Fig. 2.15 The abdominopelvic autonomic nervous system. The abdominopelvic ganglia are positioned in the center of the diagram. The sympathetic trunk is represented on the *left* and the parasympathetic input on the *right*. The *blue arrows* are thoracic splanchnic nerves. The *green arrows* are lumbar splanchnic nerves, and the *purple arrows* are sacral splanchnic nerves. Even though the lower lumbar and sacral splanchnic nerves arise from the sympathetic trunk below L2, the cell bodies of origin for these nerves are located above L2 in the spinal cord, typically found between T12 and L2

Alternatively, sympathetic fibers from the T12 to L2 spinal levels can remain in the sympathetic trunk as it courses into the pelvic basin, exiting the trunk deep in the pelvis as sacral sympathetic nerves that target the sympathetic ganglia in the inferior hypogastric plexus (Figs. 2.15 and 2.16). In the female, these sacral sympathetic fibers are located in the endopelvic fascia, under the covering of the broad ligament. Importantly, the sacral sympathetic fibers would escape transection if the presacral nerve (hypogastric plexus) were divided in the procedure termed as "presacral neurectomy" typically used for intractable pelvic pain (reviewed in [1, 18, 32]).

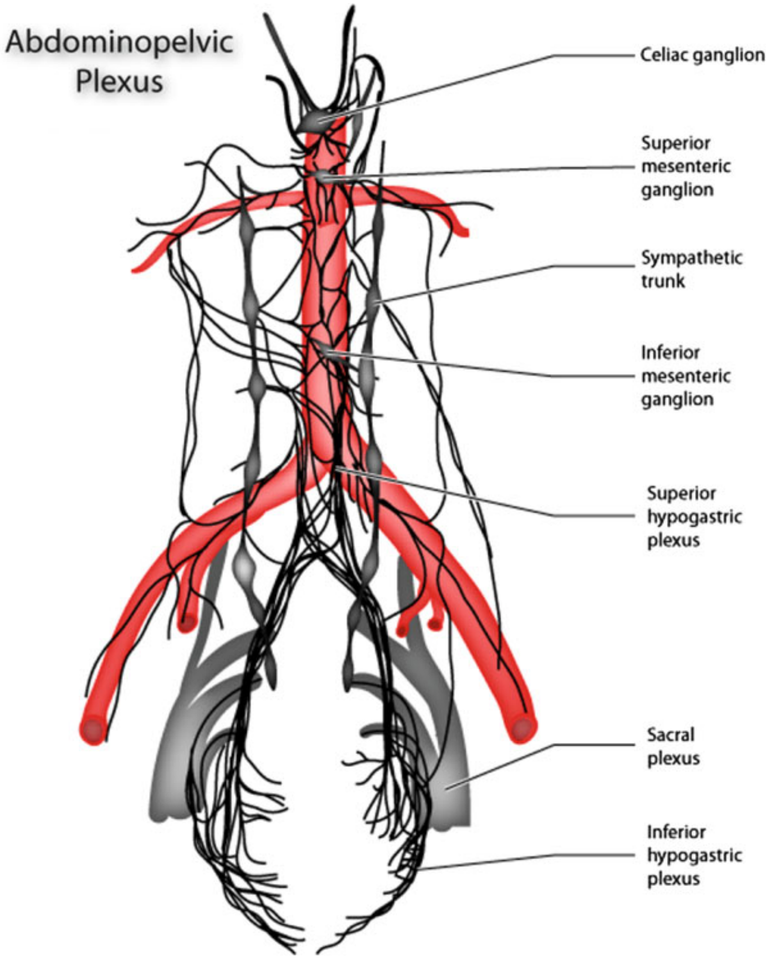

Fig. 2.16 The abdominopelvic autonomic nervous system. The abdominopelvic plexus can be seen as a complex network of fibers wrapped around the anterior and lateral aspects of the abdominal aorta and dividing just below the aorta to course in the endopelvic fascia of the pelvic basin (figure modified from reference [32])

The Pelvic Splanchnic Nerves

The pelvic splanchnic nerves (nervi erigentes) are commonly said to arise from the ventral rami of the S2–S4 nerves (Fig. 2.15) [1, 18]; however, these splanchnic nerves actually arise primarily from S3 with only small contributions from S2 or S4, but not both, and typically the secondary contribution comes from S4 only [32]. These parasympathetic nerves contribute fibers to the inferior hypogastric plexus (Figs. 2.16, 2.17, and 2.18), which is also regionally termed the pelvic plexus or Frankenhauser's plexus. It is located in the endopelvic fascia under the broad ligament and positioned on the transverse cervical ligament. The parasympathetic

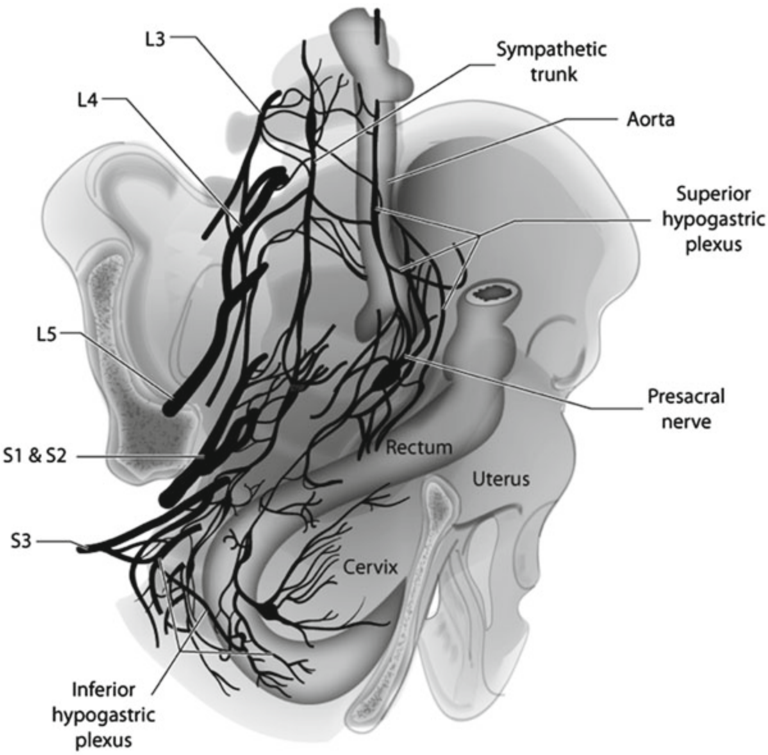

Fig. 2.17 The pelvic autonomic nervous system. This is a lateral oblique view of the female pelvis with the hypogastric plexus illustrated. The L3–S3 spinal nerves receive gray rami from the sympathetic trunk. The trunk also transmits small sacral splanchnic nerves into the hypogastric plexus. This plexus is seen along the walls of the pelvic organs (Figure modified from [32])

fibers pass through the plexus and target neurons located in ganglia on the walls of the rectum, uterus, or urinary bladder. The postganglionic fibers from these ganglia invade the layers of the target organ innervating smooth muscle and glands (reviewed in [1, 18, 32]).

The Great Abdominopelvic Plexus

The autonomic nerves and associated sensory fibers form a large plexus that extends from the thoracoabdominal diaphragm to pelvic diaphragm. This interwoven structure lies in the visceral fascia of the posterior body wall anterior to the aorta, in close juxtaposition with the aorta and its three unpaired visceral branches (Fig. 2.16): the celiac, superior mesenteric, and inferior mesenteric arteries. Clusters of prevertebral ganglia are embedded in the plexus, typically surrounding the three unpaired visceral arteries (reviewed in [1, 18, 32])

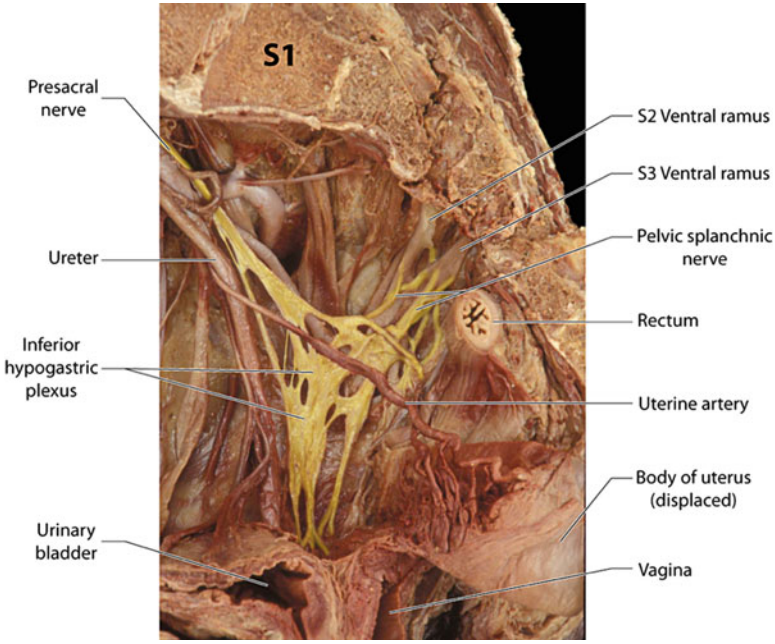

Fig. 2.18 The hypogastric plexus. This is a medial view of a sagittal section through the pelvis of a 54-year-old female. Her uterus has been displaced medially, and the broad ligament and underlying endopelvic fascia have been removed to reveal the inferior hypogastric plexus. Superiorly, the presacral nerve approaches the plexus, and inferiorly the plexus extends to the lateral wall of the bladder and the cervix by passing over the transverse cervical ligament. Posteriorly, the pelvic splanchnic nerves are seen approaching the plexus

The great abdominopelvic plexus is divided into four midline regions: celiac, superior and inferior mesenteric, and superior hypogastric plexuses located in the abdominal cavity and a fifth region in the pelvic basin, an inferior hypogastric plexus that is present laterally (Figs. 2.16 and 2.17). The distal end of the superior hypogastric plexus can taper to form a solitary band of fibers often termed the presacral nerve that passes over the sacral promontory. Opposite the body of S1, this structure divides into two laterally positioned regions [33] termed the inferior hypogastric plexus (Figs. 2.16 and 2.18). Rarely does the presacral nerve present as a well-defined structure. More typically, it is a broad tangled mass of multiple fiber bundles as seen in Fig. 2.17. The inferior hypogastric plexus lies in the endopelvic fascia on either side of the three midline pelvic organs – the rectum, the uterus, and the bladder. The plexus is covered by the broad ligament in the female. Posteriorly, the plexus receives sympathetic contributions through the tiny sacral splanchnic nerves derived from the sympathetic trunk as well as parasympathetic contributions from the larger pelvic splanchnic nerves, which branch directly from the S3 ventral ramus with additional small contributions from either S2 or S4 (Fig. 2.15; (reviewed in [1, 18, 32])).

Visceral Afferent Fibers in the Pelvic Basin

All of the various autonomic routes into the pelvic basin also serve as pathways for afferent or sensory fibers to return to the spinal cord. Typically, these visceral afferent fibers respond to noxious activity and convey the sense of pain.

Sensory fibers can often be identified in peripheral tissue by the presence of typical neurosecretory peptides such as substance P (SP), calcitonin gene-related peptide (CGRP), nitric oxide synthase (NOS), and vesicular acetylcholine transporter (VAChT). However, as of this writing, there are no specific neurochemical markers for visceral afferent fibers [35]. Most visceral afferent fibers are small unmyelinated fibers that end with a naked nerve ending [27] and are associated with A delta and C fibers [36].

Type of Stimuli Eliciting a Response from Visceral Fibers

Uniquely, visceral afferent fibers are generally unresponsive to most of the tissue-damaging stimuli that would occur in a surgical situation. Instead, these sensory fibers respond typically to pressure and distension as well as to changing tissue chemistry such as an increase in proinflammatory compounds [34]. Regardless of the type of stimulus, the predominant perception of visceral fiber activity appears to be pain and discomfort.

Both low- and high-threshold mechanoreceptors responding to pressure or distension are documented; the high-threshold fibers are most likely to be visceral nociceptors. The low-threshold fibers may not reach consciousness when activated by non-noxious stimuli; however, as the stimulus intensity rises into the noxious range, the discharge rate increases significantly, suggesting that when sufficiently activated the low-threshold fibers become nociceptors as well [35].

Chemical and thermal receptors are also present in pelvic organs but have not been studied as well as the mechanoreceptors. Chemoreceptive and mechanosensitive afferent fiber systems are present in the muscularis of the urinary bladder and involve sensory peptides derived from the urothelium [36]. Small-caliber, peptide-containing sensory fibers have been described in the myometrium and endometrium of the uterus [37], as well as in the mucosa, submucosa, muscularis, and serosa of the distal colon [38]. Visceral chemoreceptive fibers and some mechanoreceptive fibers respond to the typical proinflammatory substances or to common products of ischemia such as protons, histamine, bradykinins, prostaglandin E_2, serotonin, and potassium [35]. A category of visceral fibers has been described that will not respond to mechanostimulation unless they have been exposed to an inflammatory chemical soup. Following such exposure, the fibers sensitize and lower their thresholds of activation. These fibers have been termed silent or sleeping nociceptors [34].

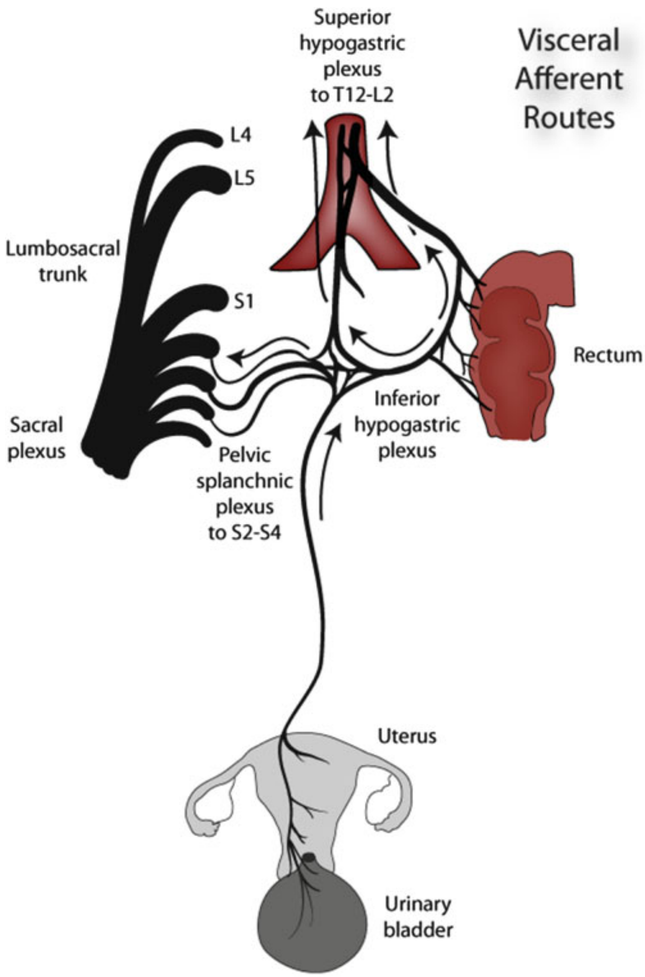

Fig. 2.19 The visceral afferent pathways of the hypogastric plexus. This diagram illustrates the flow of visceral afferent (sensory) information through the hypogastric plexus. Sensory fibers from the bladder, uterus, and colon project into the hypogastric plexus. From here, fibers can either approach the sacral spinal cord through the pelvic splanchnic nerves (*to the left*) or ascend in the hypogastric plexus to the T12–L2 level where they can use a white ramus to access the spinal nerves and the spinal cord (Figure modified from [95])

Pelvic Visceral Afferent Fibers Reach the Spinal Cord Through Several Routes

All visceral afferent fibers arising in the pelvic basin eventually reach the spinal cord by passing over a spinal nerve (Fig. 2.19). Those coursing in pelvic splanchnic nerves enter directly into the cord from spinal nerves S3 and S4. Visceral afferent

fibers in the sacral splanchnic nerves enter the sympathetic trunk and ascend to the L1–L2 level before passing through a white ramus to enter the spinal cord. Finally, visceral afferent fibers in the hypogastric plexus pass upward out of the pelvic basin, access a lumbar splanchnic nerve at L1–L2, and join the associated spinal nerves also by passage over a lumbar white ramus.

There appears to be a distinction between the input accessing the spinal cord at the thoracolumbar junction and that entering in the midsacral region. In experimental situations focused on the gastrointestinal tract, acute hollow-organ distention will strongly activate neurons in the sacral region (and brainstem vagal nuclei), whereas inflammation in the viscera activates dorsal horn neurons in both thoracolumbar and sacral regions, as well as vagal nuclei [39, 40].

Studies on the reproductive system in the rat have also documented a distinction between visceral input to the thoracolumbar and lumbosacral spinal cord [41]. Sensory fibers from the uterus and adnexal tissue typically course upward out of the pelvic basin in the hypogastric plexus to reach the thoracolumbar spinal cord, while sensory fibers from the vaginal canal gain access to the sacral spinal cord through the pelvic splanchnic nerves. The cervix is the watershed zone; from here, afferent fibers can pass to the spinal cord through both routes.

Evidence suggests that uterine nociception will pass through the hypogastric plexus in acute situations in otherwise normal rats or humans. However, in the setting of existing pathology, afferent signals from the uterus may utilize both the hypogastric plexus and the pelvic splanchnic nerves to access the spinal cord (Fig. 2.20) [42]. In behavioral studies, sensory experiences related to mating and conception were more likely to activate primary afferent fibers in the sacral nerve roots, while those involved in pregnancy and nociceptive events were more likely to activate primary afferent fibers in the hypogastric plexus traveling to the thoracolumbar spinal cord. This pattern of neural activation is in agreement with the neuroanatomy of the rat reproductive organs: the tissue below the cervix projects heavily through the pelvic splanchnic nerves, the tissue above the cervix projects sensory fibers through the hypogastric plexus, and the cervical tissue sends afferent fibers through both routes.

Pelvic Visceral Afferent Fibers Terminate in the Spinal Cord

Three observations characterize the central termination of visceral afferent fibers [34]:

1. Although few in number compared to somatic afferent fibers, visceral fibers are more divergent upon entering the spinal cord, thereby contacting multiple dorsal horn neurons.
2. Visceral afferent fibers ascend and descend many more levels than typical somatosensory afferent fibers.
3. Almost all visceral afferent fibers are convergent on dorsal horn neurons that also receive somatic primary afferent fibers.

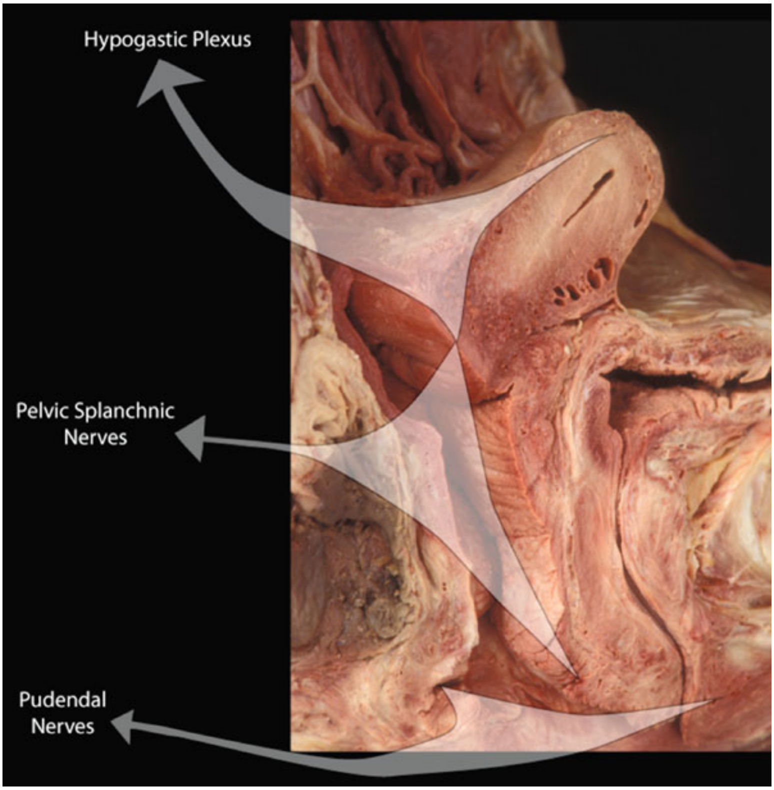

Fig. 2.20 Visceral pain pathways about the reproductive organs of the pelvis. This is a posterior-oblique view of a sagittal section of the uterus, cervix, and vagina in a 54-year-old female. The *arrows* indicate the differential flow of sensory information from these reproductive organs as described by Ruch [29]

All visceral primary afferent fibers from the pelvic basin have their cell bodies located in the dorsal root ganglia of either the thoracolumbar segments or the middle sacral segments; their central processes terminate in the dorsal and intermediate (lateral) horns of the spinal cord. As a given dorsal root approaches the spinal cord, its fibers segregate into a medial division of large fibers and a lateral division of small fibers (Fig. 2.21). The medial division fibers are well myelinated and enter into the dorsal columns, while the lateral division consists of lightly myelinated and unmyelinated fibers that enter the apex of the dorsal horn. The visceral afferent fibers are contained in the lateral division; thus, they enter the dorsal horn directly. Some of these fibers terminate in laminae I and II. However, most pass deep into the dorsal horn to terminate in lamina V, as well as in the base of the lateral horn. Finally, a few fibers extend medially to reach the area around the central canal in lamina X [43]. Visceral fibers appear to avoid much of the inner portion of lamina II and all of lamina III.

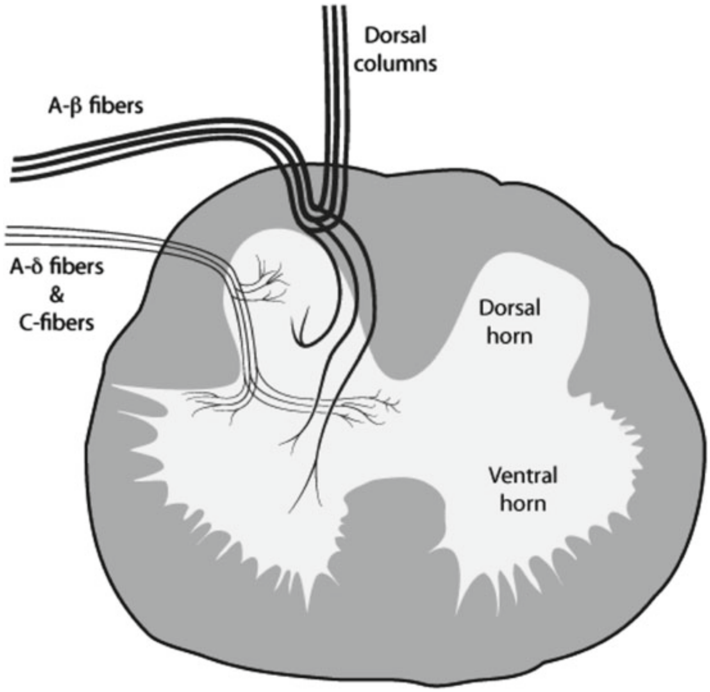

Fig. 2.21 The spinal terminations of primary afferent fibers. This is a schematic drawing of a lumbosacral spinal cord section illustrating the termination of collateral branches from large myelinated fibers and small lightly myelinated and unmyelinated fibers in the dorsal horn

Although visceral fibers in the dorsal roots are few in number (5–15%), a large percentage of spinal cord neurons respond to visceral afferent stimuli, suggesting wide-ranging distribution of visceral primary fibers in the spinal gray matter [44]. The primary afferent endings in the deep portion of the dorsal horn and the lateral horn are of much interest since it is here where visceral fibers converge with those of the somatosensory system. The distribution of visceral afferent fibers is similar to the distribution of small-caliber fibers from the deep somatic tissues such as bone, joint, and muscle [45]. However, somatic input is generally restricted to a narrow range of segments, while visceral fibers typically distribute over a wide range of segments [25]. Extensive convergence occurs between most visceral afferent systems and the deep somatic afferent systems, but there is ample evidence for viscerovisceral convergence in the dorsal horn as well [34].

A Viscerotropic Map Is Present in the Spinal Cord

A general relationship exists between the organ position in the body cavity and its innervation level in the spinal cord; this relationship forms the basis for a viscerotome. Viscerotomes are embryologically determined as detailed by Ness and Gebhart

[46]. Since significant movement of organ systems occurs during development, the arrangement of viscerotomes is not in register with the surrounding somatotomes.

In the human, the viscerotomes are initially studied by fine anatomical dissection and confirmed by examining patterns of evoked or pathological referred pain from the organ of concern. Considerable overlap exists between viscerotomes for anatomically related organs; thus, the viscerotropic maps are not precise and much viscerovisceral convergence in the spinal cord occurs. Dorsal horn neurons in each viscerotome also receive input from primary afferent fibers of somatic origin; this somatovisceral convergence is thought to underlie the existence of numerous referred pain patterns [28].

Spinal Cord Processing of Nociception from Pelvic Afferent Fibers

The patterns of neuronal activity in the dorsal horn following noxious stimulation of some visceral organs have been studied and found to share some common features with those involving somatic input [40]. The organs studied are mainly found in the gastrointestinal system and in the urinary tract. Three fundamental response patterns are seen: abrupt-onset neurons, sustained neurons, and inhibited neurons. The abrupt-onset neurons appear to be stimulus-bound, activating with the onset of the stimulus and ceasing with the stimulus offset.

Sustained neurons take longer to build to a crescendo (seconds) but will continue to discharge after cessations of the stimulus. Inhibited neurons typically cease their spontaneous activity in response to a noxious stimulus.

The activity of both abrupt and sustained neurons can be affected by modulation of the NMDA (N-methyl-D-aspartate) and AMPA (a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors, two receptor types known to be involved in the process of sensitizing dorsal horn neurons to noxious somatic stimuli [40]. The involvement of NMDA and AMPA chemistry with visceral spinal systems has prompted the suggestion that visceral hypersensitivity may utilize pathways similar to those of the well-documented central sensitization and hypersensitivity seen following repeated noxious somatic stimuli [43].

Sensitization of Primary Afferent Fibers and Their Central Pathways

When primary afferent fibers receive excessive stimuli such as in inflammation or extreme mechanical stimulation, they can undergo a process of sensitization in which their thresholds for activation drop and their response to a given stimulus increases [47, 48]. It is now clear that sensitization can occur, not only at the dorsal horn, but also at multiple levels in the nervous system [49]. Peripheral sensitization can produce an expanded local area of increased sensitivity, a process termed peripheral sensitization.

Spinal cord neurons receiving excessive input from a given peripheral fiber or convergent inputs from multiple peripheral fibers can undergo a process of central sensitization, which can produce hypersensitivity in a whole region of a body such as in a portion of a limb or a complete limb [50]. Evidence is accumulating to support the concept that sensitization may also occur at a higher level in the central nervous system such as in the anterior cingulate cortex [51] and the amygdala [52]. Such forebrain sensitization can result in hyperresponsiveness expressed throughout the entire system, a process that may be involved in such diffuse pain disorders as fibromyalgia.

That sensitization can occur involving the visceral sensory system has been suggested in numerous studies. In one such example, repeated stimuli delivered to a healthy organ can lead to increasing intensity of perceived pain [44]. The existence of sensitization at multiple levels in the somatic and visceral sensory systems can explain some of the progressively worsening patterns of chronic pain that can accompany dysfuction in the somatic and visceral pelvis.

Influence of Visceral Afferent Fibers on the Dorsal Horn of the Spinal Cord

A strong interaction exists between the visceral and somatic sensory systems in the dorsal horn of the spinal cord. Most dorsal horn neurons with receptive fields in the viscera can also be activated by somatic stimuli; thus, the visceral sensory system of the spinal cord is almost completely convergent with somatic systems. The combination of the two or more differing forms of input – one of visceral and one of somatic origin – to a population of dorsal horn neurons could contribute to enhanced sensitization and facilitation through a mechanism such as that described for somato-somatic convergence by Zimmermann [53]. Furthermore, cross-reaction between visceral organs can occur; repetitive stimuli delivered to one organ can lead to sensitization of surrounding organs such as repetitive noxious stimuli applied to the sigmoid colon sensitizing the rectum to innocuous stimuli [54].

Convergence of somatic (skin and muscle) and visceral information on visceroceptive neurons in the dorsal horn is a key characteristic of referred pain [28] and of viscerosomatic reflexes [35] such as the paraspinal muscle spasms seen associated with strong input from experimentally induced inflammatory events in the rat uterus [55, 56]. Observations in humans document the presence of somatic hyperalgesia and trophic changes secondary to intense visceral noxious stimuli from the urinary bladder suggesting the presence of viscerosomatic reflexes [25, 57]. In fact, the degree and location of somatic response appear to be strongly related to the underlying visceral dysfunction. The longer the chronic pain patterns exist, the greater the degree of change in the associated somatic tissue, and the location of the somatic change appears to map closely to the appropriate viscerotomes [58]. Some of the somatotropic and vasodynamic changes reported following both acute and chronic uterine or bladder pain patterns may have their origin in a series of dorsal root reflexes such as those described by Sluka and Willis [59, 60].

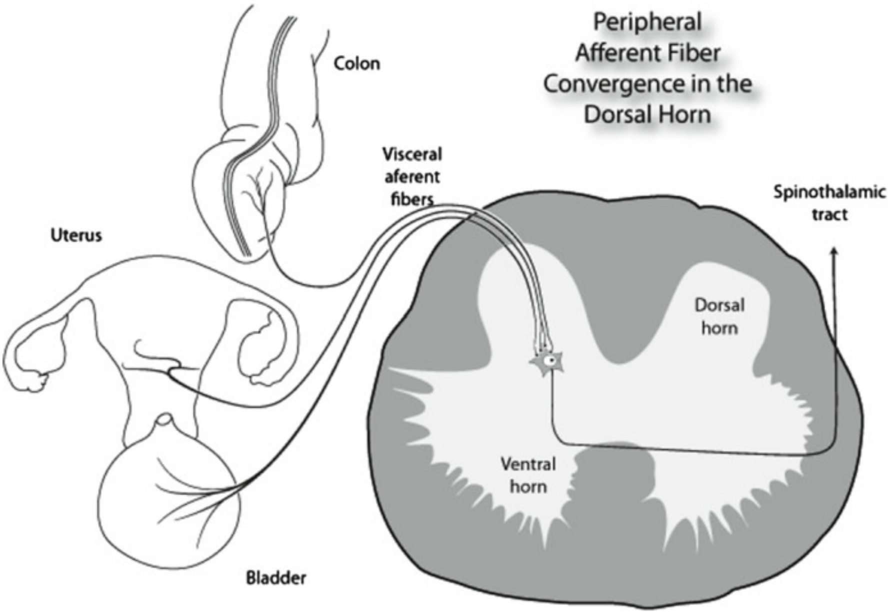

Fig. 2.22 The convergence of visceral afferent pathways in the dorsal horn of the spinal cord. This is a schematic diagram of the lumbosacral spinal cord illustrating the convergence of multiple small-caliber fiber systems on neurons in the deep portions of the dorsal horn. This convergence is thought to underlie the cross-organ interactions seen in specific pain patterns [63]

Along with cross talk between visceral and somatic systems, there appears to be ample evidence for viscerovisceral interaction (Fig. 2.22). The clinical observation that dysfunction in one internal organ can enhance the pain and hyperalgesia generated by a second organ has long been known [61]. The transient increase in pain perception associated with specific stages of the menstrual cycle is well documented [56]; specific examples include the exacerbation of discomfort in associations between irritable bowel syndrome and dysmenorrhea or between dysmenorrhea and urinary calculus. Suggested mechanisms for viscerovisceral cross-talk include such processes as the spread of neurogenic inflammation between organs of close juxtaposition, the sensitization of peripheral afferent fibers and their convergence onto common neurons in the dorsal horn, the sensitization of visceroreceptive neurons in the spinal cord, and the development of sensitized convergent neurons in brainstem, thalamus, or forebrain structures such as the amygdala [62].

In the reproductive organs, experimentally induced inflammation of the uterus in a rat resulted in signs of enhanced inflammation in surrounding non-treated organs such as the urinary bladder; this response was abolished by section of the hypogastric plexus [63]. Based on these results, it would appear that at least a portion of the cross talk between organ systems in the pelvis involves a neural reflex through the hypogastric plexus and the release of proinflammatory substances in the non-treated organ supports a mechanism utilizing dorsal root reflexes.

Ascending Pathways Involved in Pelvic Pain

Anterolateral System

The classical ascending pathway for somatic nociception involves the synaptic termination of the primary afferent fiber in the dorsal horn (Fig. 2.23). The postsynaptic neuron sends its axon through the anterior white commissure to the contralateral

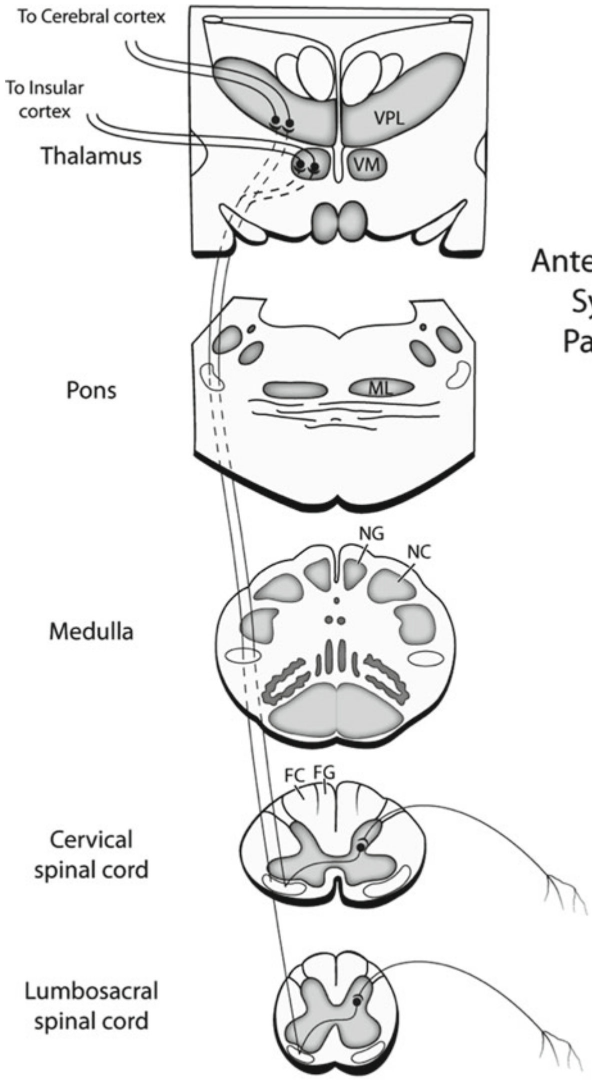

Fig. 2.23 The anterolateral system. This is the classic system of ascending information in the small-fiber systems of the spinal cord such as that derived from A delta and C fibers (Figure modified from [97])

anterolateral system at or slightly above the level of the dorsal horn neuron. Axons in the anterolateral system ascend to terminate in the medulla, pons, midbrain, hypothalamus, and thalamus. In the medulla, a major target of ascending somatic and visceral sensory information is the solitary nucleus of the vagal complex [64]; however, much of this input is related to reflex actions as opposed to nociception and pain perception.

Although some visceral nociceptive information ascends in this classic spinothalamic system to the thalamus, it does not appear to be the major route for this information from the pelvis. Instead, a significant portion of the pelvic nociceptive input ascends the spinal cord close to the midline in a postsynaptic dorsal column pathway [65–67].

Postsynaptic Dorsal Column System

The dorsal columns of the spinal cord have long been described as carrying the axons of well-myelinated cutaneous touch receptors whose cell bodies are found in the ipsilateral dorsal root ganglia (Fig. 2.24) [68]. However, a postsynaptic system present in the dorsal columns has also been well documented in the literature [69]. For example, many fibers of sacral origin in the dorsal columns appear to arise not from dorsal root ganglion cells but from ipsilateral dorsal horn neurons and to be involved with nociceptive visceral sensory information. Since the visceral pathway has a synapse present in the dorsal horn, it is termed a postsynaptic pathway.

The postsynaptic pathway appears to be topographically organized similar to the myelinated fibers of the dorsal columns; that is, thoracic fibers near the dorsal intermediate septum and the sacral fibers project medially in the fasciculus gracilis to the nucleus gracilis (Fig. 2.25) [70]. Pelvic splanchnic nerve input to the sacral spinal cord is relayed through dorsal horn neurons that project axons upward to reach the nucleus gracilis; from here, a second synaptic relay occurs to the ventroposterior lateral thalamic nucleus (VPL) [71]. Neurons in and around the VPL were responsive to both colorectal distention and cutaneous touch suggesting convergence of visceral and somatic input into these forebrain neurons [65, 72].

Experimental inflammation of the colon resulted in facilitation of the VPL neurons to noxious colorectal distension but did not significantly change the response of these neurons to cutaneous stimuli [73]. The presence of the postsynaptic dorsal column pathway for visceral pelvic pain helps explain the amelioration of intractable pelvic pain patterns following midline myelotomies in the lower thoracic region that damaged the medial aspect of the fasciculus gracilis [70].

Hormonal Associations

A growing body of evidence supports the concept that a sexual dimorphism exists in the perception of pain and that females, as a group, are more sensitive to pain and more prone to developing various chronic pain syndromes [40, 74, 75].

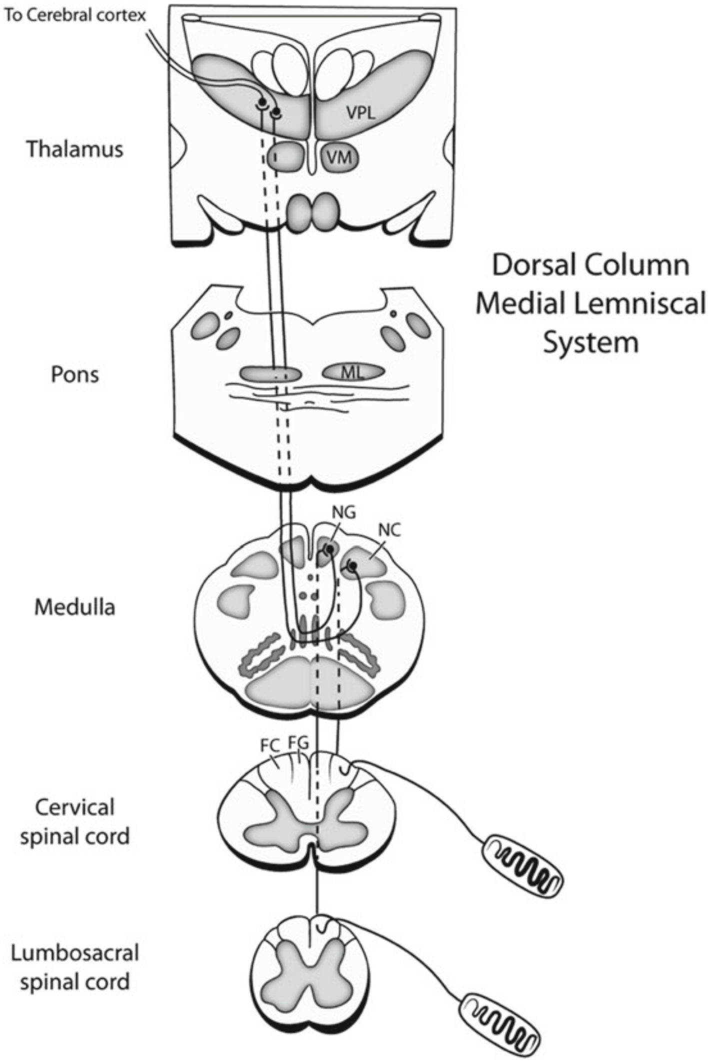

Fig. 2.24 The dorsal column-medial lemniscal pathway. This is the classic system of ascending information in the large-fiber systems of the spinal cord such as that derived from the A beta cutaneous touch corpuscles (Figure modified from [97])

The pathophysiology for this sexual dimorphism is yet to be clearly defined. Along with the influence of sex steroids, consideration must also be given to other factors such as age, environment, history of physical or emotional abuse, and comorbid conditions like sleep disorders. To date, however, there exists strong evidence pointing to a significant role of the estrogens in increasing the sensitivity of primary afferent nociceptors as well as dorsal horn neurons in the spinal cord (see Chap. 1).

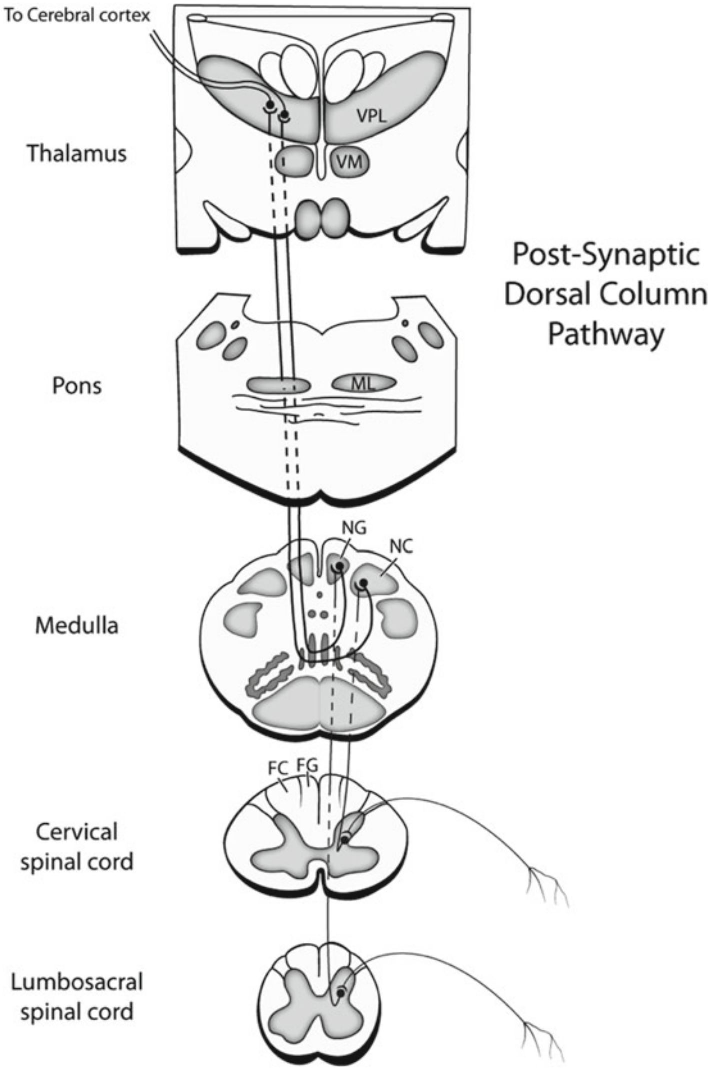

Fig. 2.25 The postsynaptic dorsal column pathway. Compare this diagram to that of Fig. 2.24; in the postsynaptic pathway, dorsal horn neurons receive information from small-caliber visceral afferent fibers and project their axons upward in the dorsal columns to reach the dorsal column nuclei in the medulla. Although the dorsal columns were traditionally thought of as carrying discriminative sensory information and proprioception, it is now apparent that they also carry visceral noxious sensations in the postsynaptic pathway as well (Figure modified from [97])

Estrogen receptors are present on cells that are involved in the peripheral as well as spinal and forebrain mechanisms for processing nociceptive information. Although much of the experimental work was done using colorectal distension as a model, several studies have addressed the suppressive influence of estrogen on the

ability of morphine to attenuate the reflex responses generated by uterine-cervical distention [76].

A strong argument supporting the role of sex steroids in increased sensitivity to noxious stimuli is found in the fluctuation of sensitivity with the phase of the menstrual cycle [63, 75]. Interestingly, in the study by Winnard and coworkers, the experimentally induced inflammation in one pelvic organ induced inflammation in other pelvic organs. This reflex response was dependent on the intact condition of the hypogastric plexus and varied in potency with the phase of the estrous cycle in the rat. This neuronally dependent, cross-organ spread of inflammation supports a possible role for dorsal root reflexes and suggests that the neurogenic inflammatory process may be strongly modulated by sex steroids.

It is known that estrogens have a diverse influence on many of the biological pathways leading to inflammation and nociception [74]. Although there is a large body of information supporting the concept that estrogen can enhance sensitization to a noxious stimulus [40], it is not certain where this enhancement occurs: in the periphery of the nervous system, in the spinal cord, at supraspinal levels, or in some combination of all levels. However, it is becoming apparent that the mechanism behind this relationship between sex steroids and pain perception is intimately tied to how the brain processes pain, and our knowledge of that field is just beginning to crystallize.

Forebrain Areas Involved in Pelvic Pain

Nociceptive input from various tracts in the spinal cord relays through the thalamus, eventually to be mapped on the cerebral cortex. The distribution of forebrain areas that demonstrate altered neural activity to a painful stimulus has been termed a body-self neuromatrix for the integration of the multiple inputs resulting in the perception of pain [77] or simply “central pain matrix” [78, 79].

The processing of nociceptive information and the generation of the feelings of pain can be thought of as involving three separate but interconnected aspects of the forebrain pain matrix:

Sensory/discriminative
Cognitive/behavioral
Affective/motivational

While the first component (sensory/discriminative) allows for the localization and description of the pain, the second component (cognitive/behavioral) allows for the understanding of the pain. The third component (affective/motivational) brings in the emotional aspect of the pain, relating the current pain to past experiences and feelings.

Significant numbers of studies have examined the pain matrix created by noxious stimuli expressed on somatic tissue [48, 80]. The forebrain regions responding most reliably to noxious somatic stimuli include primary and secondary somatic

sensory cortex, motor cortex, supplementary motor cortex, insular cortex, anterior portions of the cingulate cortex, posterior parietal cortex, prefrontal cortex, thalamus, as well as regions involving the amygdala and less often the basal ganglia and cerebellum [79]. To date, the few studies examining visceral pain representation in the forebrain show a fundamental pain matrix of cortical activity that is essentially the same for either somatic or visceral stimuli with certain differences [81].

The distinctions between evoked neural patterns from somatic and visceral noxious stimuli of matched perceived intensity are focused on intensity of neural response rather than its forebrain location. Thus, visceral noxious stimuli tend to produce more activity in such areas as the insular cortex and the anterior cingulate cortex, both regions known to be involved in the autonomic response and the emotive response, respectively, to harmful or potentially harmful stimuli [34].

It is apparent that visceral pain is more adept at activating the affective/motivational component of the pain matrix. This is in line with the observations that visceral stimuli are better at evoking an emotional response than equivalent somatic stimuli [56]. A significant structure of the affective/motivational component is the amygdala [82], a region of the brain associated with negative feelings, fear memories, and a strong drive on numerous brainstem regions including the arousal system.

Amygdala

The amygdala is located in the medial portion of the temporal lobe, rostral to the hippocampus, and is composed of multiple nuclei whose precise borders are still in dispute [83]. The role of the amygdala in receiving adverse stimuli and generating a fear response is becoming reasonably well known [84, 85]. Of particular interest is the spinal input to the amygdala related to nociception [82, 86].

Spinal input to portions of the amygdala can facilitate neurons, resulting in a change of activity that is essentially a form of central sensitization. This response is similar to the central sensitization that occurs in the dorsal horn of the spinal cord to an intense nociceptive stimulus and has been described as sensitization at a supraspinal level. Importantly, the sensitization in the amygdala has been seen to accompany visceral pain paradigms [87] as well as arthritic pain [88] and neuropathic pain [89]. The anatomy, connectivity, and response properties of the amygdala strongly support a role for this region of the forebrain in the emotional-affective dimension of pain.

Descending Pathways Regulating Pelvic Pain

The transmission of nociceptive information through the spinal cord and into forebrain structures is modulated by a complex array of descending systems capable of

significantly controlling the amount of pain experienced by the individual [90–93]. One of these descending systems involves the midbrain (periaqueductal gray) and the rostral ventromedial medulla, while a second descending system arises dorsolaterally at the pontomedullary junction and includes such structures as the locus coeruleus (adrenergic fibers). Both of these pathways contain axons that terminate in the dorsal horn of the spinal cord and can influence the transmission between primary afferent fibers and second-order ascending tract neurons. Interestingly, in the descending system from the rostral ventromedial medulla, there are neurons present that can either suppress nociceptive transmission in the dorsal horn (OFF-cells) or facilitate nociceptive transmission (ON-cells).

Thus, the so-called endogenous pain control systems can function to either suppress the processing of nociceptive information at the spinal cord level reducing the pain experience or to enhance this transmission, thereby making the patient experience more pain [90–93]. Recent experimental studies suggest that the brainstem nuclei controlling the descending systems can become facilitated consequent to prolonged stimulation in a manner similar to that seen in the sensitization of dorsal horn neurons. In such a case, it has been suggested that facilitation of that portion of the system that enhances the perception of pain could be an important step in the development of persistent or chronic (maldynic) pelvic pain patterns [92].

Finally, what controls the pain control systems? From numerous studies, it appears that the brainstem nuclei involved in the modulation of pain receive their input in part from such regions as the hypothalamus, amygdala, and anterior cingulate cortex. Through this organization, the emotional portion of the brain can exert a direct influence over our perception of pain [82].

Since the activity of such regions as the amygdala and cingulate cortex is a summation of a lifetime of experiences, it allows the past to strongly color our perception of current events. Painful stimuli are known to activate the amygdala and contribute to its facilitation. In this fashion, a mildly painful event – which would otherwise pass with little attention or concern – when imposed on sensitized neurons in the amygdala could become grossly magnified through enhanced processing of nociceptive information in the spinal cord. The resultant enhanced ascending input to the amygdala further increases anxiety as well as facilitates obsession with the pain. This represents a feed-forward situation, increasing the facilitation in the forebrain and exacerbating and prolonging the pain pattern (Fig. 2.26).

Thus, past emotional events such as trauma or abuse could, through a process of facilitation at multiple levels in the nervous system, drive, in part, both the initiation of pain patterns as well as the development of persistent pain from pelvic dysfunctions (see Chap. 11). Finally, through the close connections between the amygdala and the prefrontal cortex, especially the ventromedial and orbital portions, emotional activity can influence cognitive decisions and alter patterns of behavior [94].

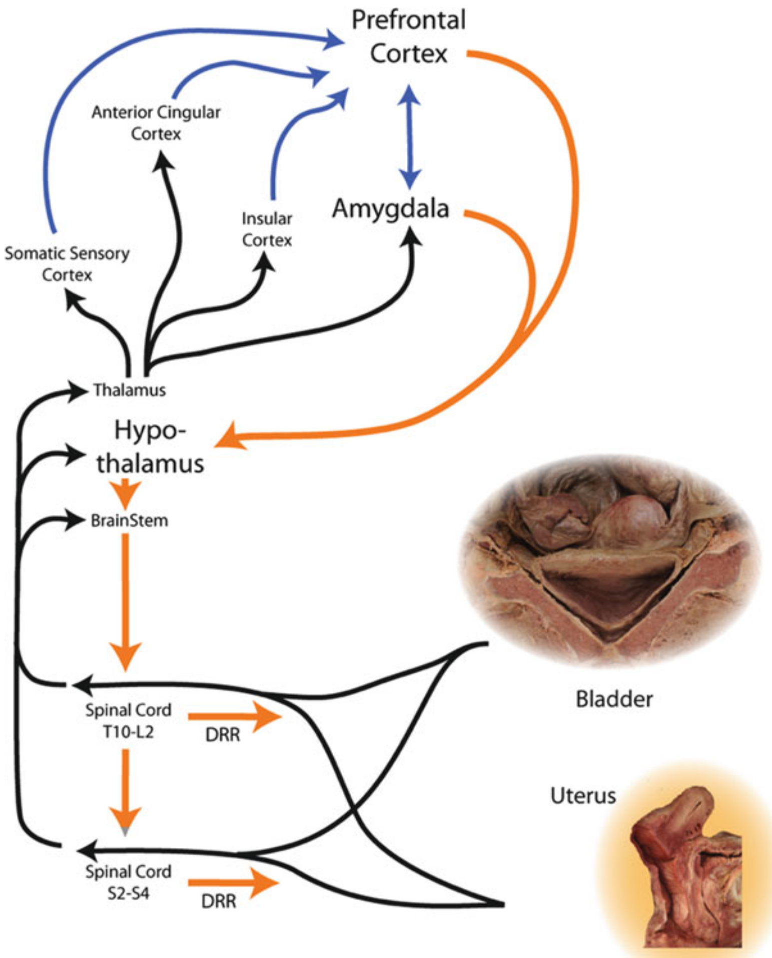

Fig. 2.26 Forebrain modulation of visceral pain. The *black arrows* indicate the ascending flow of sensory information from the pelvic visceral structures. The *blue arrows* indicate forebrain pathways for processing the visceral sensory information. The *orange arrows* indicate the pathways through which the forebrain structures modify the processing of pain in the brainstem and spinal cord structures. Finally, the orange arrows marked DRR (dorsal root reflexes) suggest that forebrain structures may be able to influence the activity of pathological situations in the peripheral tissues through the release of proinflammatory peptides from the visceral primary afferent fibers

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Chapter 3
Fibromyalgia and Myofascial Pain

Joseph F. Audette

Introduction

The soft tissue pain syndromes are among the most nebulous and yet arguably most prevalent conditions encountered in pain medicine. Although not progressive, degenerative, or life threatening in their effects, they can cause significant pain and functional limitations for patients. In addition, because of the absence of imaging findings or other objective diagnostic testing available, the diagnosis (and often treatment) of these conditions is highly dependent on the clinical skills of the clinician. Therefore, it is vital that the clinician seeing patients with pain issues be comfortable with the evaluation and management of patients with these disorders.

Fibromyalgia

Fibromyalgia (FM) is a chronic pain disorder characterized by widespread soft tissue pain that is currently understood to be secondary to alteration in central pain processing. The presence of individuals with widespread soft tissue pain is not a recent development. During the sixteenth century, Guillaume de Baillou from the medical faculty at the University of Paris introduced the term muscular rheumatism to describe soft tissue pain [1]. At the beginning of the nineteenth century, Balfour and Scudamore first voiced the concept that soft tissue pain arises as a result of inflammation in the fibrous connective tissue of skeletal muscle [2, 3]. In 1904,

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Table 3.1 Other functional syndromes commonly associated with fibromyalgia

Chronic fatigue syndrome
Irritable bowel syndrome and other functional gastrointestinal disorders
Temporomandibular joint disorder
Restless leg syndrome and periodic limb movements in sleep
Idiopathic low back pain
Multiple chemical sensitivity
Primary dysmenorrhea
Headache (tension greater than migraine, mixed)
Migraine
Interstitial cystitis/chronic prostatitis/painful bladder syndrome
Chronic pelvic pain and endometriosis
Myofascial pain syndrome/regional soft tissue pain syndrome

Sir William Gowers coined the term "fibrositis" to describe patients with widespread pain of the fibrous tissue and overlying muscles [4].

Over time, given the lack of clear evidence that there was an inflammatory condition in the soft tissues, the prevailing theory changed to view FM as a type of psychosomatic illness. Hudson argued that fibrositis was a variant of depression and coined the term "affective spectrum disorder" [5, 6]. Since that time, given the growth in research in pain processing, together with the recognition that a variety of other functional comorbidities commonly coexist with FM, such as temporomandibular joint disorder and irritable bowel syndrome, among others (see Table 3.1), it has become clear that FM is neither a variant form of depression nor is it a primary muscle disorder but can be best understood as a disorder of central pain processing that can lead to widespread, multisystem sensitization [7, 8].

This condition has been also referred to as central sensitivity syndrome. Ablin and others have highlighted some of the key features of this disorder [9]:

- Multifocal pain, fatigue, insomnia, cognitive or memory problems, and in many cases psychological symptoms.
- No objective tissue pathology or gold standard to anchor disease.
- Syndromes occur approximately 1.5–2 times more commonly in women than men (even higher rates in tertiary pain settings).
- Strong familial predisposition to these symptoms and illnesses.
- Somatic symptoms and syndromes are separable from depression and other psychiatric disorders.
- A variety of biologic stressors seem to be capable of triggering or exacerbating these symptoms and illnesses, including physical trauma, infections, early life stress, and deployment to war, in addition to some types of psychological distress.
- The presence of neurogenic inflammation, dysfunction of the autonomic nervous system, and hypothalamic-pituitary dysfunction.

The prevalence of FM in the United States has been estimated at 3.4% of women and 0.5% of men, for a total of 3.7 million Americans [10]. The average age of onset is between 30 and 50 with the peak ages found in woman 50–59 years of age [11].

Table 3.2 Location of fibromyalgia tender points

Occiput: suboccipital muscle insertions
Trapezius: midpoint of the upper border
Supraspinatus: above the medial border of the scapular spine
Gluteal: upper outer quadrants of buttocks
Greater trochanter: posterior to the trochanteric prominence
Low cervical: anterior aspects of the intertransverse spaces at C5–C7
Second rib: second costochondral junctions
Lateral epicondyle: 2 cm distal to the epicondyles
Knee: medial fat pad proximal to the joint line

Adapted from the American College of Rheumatology (1990)

The diagnosis of FM is based on the American College of Rheumatology criteria that consist of at least a 3-month history of widespread pain that is bilateral and includes the upper and lower body and spine, as well as the presence of excessive tenderness when 4 kg/cm^2 of pressure is applied to 11 of 18 muscle and tendon sites listed in Table 3.2 [12]. Although women are only 1.5 times more likely to have widespread pain than men, they are 10 times more likely to have 11 out of 18 tender points consistent with the ACR diagnostic criteria [13]. Recognizing associated syndromes – such as irritable bowel/bladder syndrome, restless leg syndrome, dysautonomia, endocrine dysfunction, cognitive dysfunction, dizziness, cold intolerance, headaches, temporomandibular disorder (TMD), chronic pelvic pain, multiple chemical sensitivity, and mood disorders – is integral to being able to guide patients toward successful functional improvement and treatment. In addition, it is important to recognize that patients with FM are more likely to have a number of other associated medical problems when compared to patients with other rheumatic conditions. These include hypertension, environmental allergies, asthma, gastrointestinal issues, pulmonary disorders, cancer, thyroid dysfunction, and bladder and gall bladder dysfunction [14]. Obesity and sleep apnea are also more common in FM patients than control subjects [15, 16].

According to the ACR diagnostic criteria, FM is a diagnosis of inclusion. Thus, other rheumatologic conditions such as systemic lupus erythematosus, rheumatoid arthritis, and osteoarthritis can co-occur with FM and, if suspected, may require further evaluation, treatment, or specialty referral. In Europe, however, consensus diagnostic criteria for fibromyalgia differ from the US model. In 1990, Müller and Lautenschlager defined fibromyalgia as pain in the musculature and tendon insertions in at least three body locations of at least 3 months duration with increased pain sensitivity at 12/24 points with 2 kg/cm^2 of force, associated with autonomic and functional disturbances, psychological comorbidities, and normal laboratory tests. Therefore, based on the European guidelines, FM is considered a diagnosis of exclusion that is made after ruling out other potential causes of widespread pain [17].

In fact, it has been demonstrated that individuals with fibromyalgia have diffuse sensitivity to normal pressure stimuli that go beyond the defined diagnostic tender point locations [13]. In addition to the heightened sensitivity to pressure, fibromyalgia patients also display a decreased threshold to heat [18], cold [19], and electrical

stimuli [20]. Wolfe argues, as have others, that the goal of the tender point assessment is not to diagnose a discrete condition (fibromyalgia), but it is best used to assess the degree of sensitization, or "fibromyalgianess," regardless of the pain generator [21]. Therefore, whether a patient has rheumatoid arthritis, osteoarthritis, or TMD, the assessment of pressure pain threshold on typical fibromyalgia tender points provides important clinical information about the need for aggressive treatment of a centrally facilitated state.

Like many chronic pain syndromes, the diagnosis of FM is based on the evaluation of subjective symptoms and is lacking in specific and unique pathophysiological characteristics. Thus, the nature and existence of illnesses such as FM are often questioned, and the symptom complex associated with these conditions is commonly attributed to psychological factors. Individuals with FM have approximately a six to seven times greater risk for the co-occurrence of mood disorders when compared to first-degree relatives without FM and to a cohort of patients diagnosed with rheumatoid arthritis and their first-degree relatives [22]. These findings have led to speculation that FM should be considered a stress-related or somatoform disorder. There is also a strong genetic predisposition for FM, with an odds ratio of 8 in family members of fibromyalgia patients, with the same family members also having an increased risk for depression [23]. However, in twin studies of individuals with chronic widespread pain, the presence of a mood disorder in one twin did not increase the risk in the other twin, although there was a significantly increased risk for certain comorbidities associated with fibromyalgia, such as temporomandibular joint dysfunction and irritable bowel syndrome [24]. In population-based studies, both major depression and anxiety disorders increase the risk for having pain. However, the existence of psychological disorders in population studies of respondents with widespread pain was not significantly higher than in control groups [25, 26]. In contrast, studies of patients with fibromyalgia that present to rheumatology clinics have demonstrated significantly higher incidence of psychiatric comorbidities when compared to a community-based population of individuals who meet the ACR criteria for FM but had not sought medical care [27].

As a result of twin studies and population surveys, the risk of developing FM is now estimated to be 50% genetic and 50% of environmental origin [9]. Potential environmental triggers include early childhood stress such as neglect and/or abuse (see Chap. 11), physical traumas, and infections, such as hepatitis C, Epstein-Barr virus, parvovirus, and Lyme disease, as well as emotional stress. Of note, each of these stressors is estimated to lead to chronic widespread pain in approximately 5–10% of individuals who are exposed; the overwhelming majority of individuals who experience these same environmental stimuli will regain or maintain their baseline state of health [28].

An individual's response to stress includes activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is accomplished by the secretion of corticotropin-releasing hormone and arginine vasopressin from the paraventricular nucleus of the hypothalamus. The interaction of these neurohormones with specific receptors on corticotropic cells of the anterior pituitary causes the release of adrenocorticotropin (ACTH) that in turn stimulates secretion of cortisol from the adrenal cortex.

McEwen has characterized an organism's response to stress as allostasis [29, 30]. Allostasis is the active process that leads to adaptation to stressors and other emotional and physical challenges and involves a number of complex positive and negative feedback loops between the brain and the hypothalamic-pituitary-adrenal axis. Dysregulation of the layered feedback networks or overuse of the mediators of allostasis leads to a wear-and-tear phenomenon called allostatic load. Prolonged allostatic load can cause dysfunction of the HPA and pain modulatory systems, eventually leading to premature aging and widespread pain conditions. There is evidence of dysregulation of the HPA axis in FM. In particular, FM patients tend to show an exaggerated response of adrenocorticotrophic hormone (ACTH) with relatively blunted cortisol release in response to physiological stress [31]. The hypofunctioning HPA axis may explain findings that FM patients have lower than normal growth hormone secretion, which in turn leads to a low level of insulin-like growth hormone IGF-1. Many of the symptoms experienced by FM patients, including fatigue, arthralgias and myalgias, immunological disturbances, and sleep and mood alteration, may be directly related to the altered functioning of the HPA axis.

The response of the allostatic mechanism is influenced by hormones, in particular estrogen. For example, the synaptic and structural development of the hippocampus is strongly affected by exposure to estrogen in neonates. This may influence the female's brain response to stress, being more likely to lay down strong memories of emotionally or physically stressful events, which could lead over time to excessive allostatic load [30, 32]. In particular, in a study of women with FM, those with a history of physical or sexual abuse were found to have significantly lower levels of cerebrospinal fluid corticotropin-releasing hormone (CRH) consistent with an inability to mount an adequate cortisol response in reaction to stress [33].

In addition to the sex-related difference in the allostatic mechanism, there may be a certain subset of the population who are genetically predisposed to develop central sensitization when put under a strong environmental stress. There is a growing understanding of the genetic influence on pain sensitivity. For example, the val158met polymorphism has been found to be responsible for altered pain sensitivity in humans and works in part by modulating the activity of opioid receptors. Diatchenko and Maixner used haplotype analyses to identify three subsets of individuals based on the findings in four single-nucleotide polymorphisms termed low (LPS), average (APS), and high pain-sensitive (HPS) groups [34]. In animal models, the LPS haplotype produced much higher levels of COMT (catecholamine o-methyltransferase) enzymatic activity when compared with the APS or HPS haplotypes. The COMT enzyme is responsible for catecholamine degradation as well as influencing beta-2 and beta-3 adrenergic receptor activity. These studies showed that COMT inhibition caused a profound increase in pain sensitivity. Depressed COMT activity results in enhanced mechanical and thermal pain sensitivity in rats, which can be blocked by the nonselective beta-adrenergic antagonist propranolol. In a prospective study of 240 pain-free individuals who were phenotyped at baseline and followed for 3 years to determine who would develop temporomandibular joint disorder, it was found that carriers of the HPS haplotype were three times as likely as others to develop this condition [35]. The COMT and other genetic polymorphisms, including the serotonin

5-HT2A receptor polymorphism T/T phenotype, serotonin (5HT) transporter, and the dopamine-4 receptor, have been shown to be more prevalent in FM patients than controls [36–39].

There are a number of other lines of evidence to suggest that fibromyalgia has a physiological basis. For example, increases in the CSF levels of substance P, glutamate, nerve growth factor, and brain-derived neurotrophic factor, as well as low levels of the metabolites of serotonin, norepinephrine, and dopamine have all been identified in patients with FM [40]. All of these changes have independently been shown to adversely influence pain modulation. In addition, a growing body of evidence using brain imaging with functional MRI has provided objective support of abnormal pain processing in patients with FMS. In a study by Gracely et al., patients with FM were compared to an age- and sex-matched healthy control (HC) group. It was found that a stimulus of 4.5 kg/cm^2 of pressure was needed in the HC group to cause the same degree of pain and pattern of brain activation that was seen in the FM group when only 2.4 kg/cm^2 of pressure was applied. The enhanced brain response in FM subjects to minimal or normally nonpainful pressure provides an objective brain correlate of mechanical allodynia [41].

In a study using mu-opioid receptor (MOR) positron emission tomography comparing 17 FM patients and 17 age- and sex-matched healthy controls, FM patients displayed reduced MOR binding potential (BP) in several brain regions involved in pain modulation, including the nucleus accumbens, the amygdala, and the dorsal cingulate gyrus. MOR BP in the nucleus accumbens of FM patients was negatively correlated with affective pain ratings. Moreover, MOR BP throughout the cingulate gyrus and striatum was also negatively correlated with the relative amount of affective pain. These findings indicate altered endogenous opioid analgesic responsiveness in FM [42].

There is strong evidence that in addition to endocrine dysregulation, immune dysfunction is also likely to play a key role in the pain experience of FM patients. Recognition that the immune modulatory system plays a critical role in pain first came to the forefront in the 1980s when interleukin-2 (IL-2) and interferon alpha (IF-α) became part of certain cancer treatments. Patients treated with IL-2 and IF-α began to report diffuse myalgias and arthralgias similar to patients with FM [43]. Recently, FM patients were found to have significantly higher levels of interleukin-8 (IL-8) than control subjects. Interestingly, treatment in a multidisciplinary pain program brought IL-8 levels down but not to the levels of a control group [44].

Due to the sum of evidence discussed above, it is no longer a viable construct to attribute the enhanced pain and other symptoms of FM solely to a mood disorder. Even with the acknowledgement that stress, both physical and psychological, plays a critical environmental role in revealing the genetic tendency to develop widespread pain and its other associated comorbidities, it is not adequate, on a clinical basis, to treat the resultant pain condition as purely a stress disorder. In particular, there is a growing body of evidence that the complex multisystem presentation seen in FM patients is the phenotypical expression of a complex dysregulation of the immune and endocrine functions of FM patients that leads to pathological alterations in both cortical and spinal pain modulatory pathways.

Myofascial Pain

As part of the discussion of soft tissue pain disorders, the relationship between more localized and widespread soft tissue pain is of interest [45]. Myofascial pain is defined as pain that arises from discrete, hyperirritable palpable nodules in taut bands of muscle called myofascial trigger points (MTrPs) that have prototypical patterns of referral to areas remote from the area of muscle dysfunction (see Figs. 3.1 and 3.2) [46]. Similar to the disagreement surrounding the diagnosis of FM, the presence of this type of muscle dysfunction as a cause of pain is not without controversy, given the lack of objective tests or imaging to verify its presence. Diagnosis depends upon systematic palpation of the soft tissue by an experienced examiner following a thorough medical history (see Table 3.3). In a community-based chronic pain clinic, Gerwin et al. found that MTrPs were the primary source of pain in 74% of 96 patients who presented with musculoskeletal pain complaints [47]. Fishbain et al. found that MTrPs were the primary source of pain in 85% of 283 patients consecutively admitted to a comprehensive pain center [48]. Myofascial trigger points should be considered in the differential diagnosis of any musculoskeletal

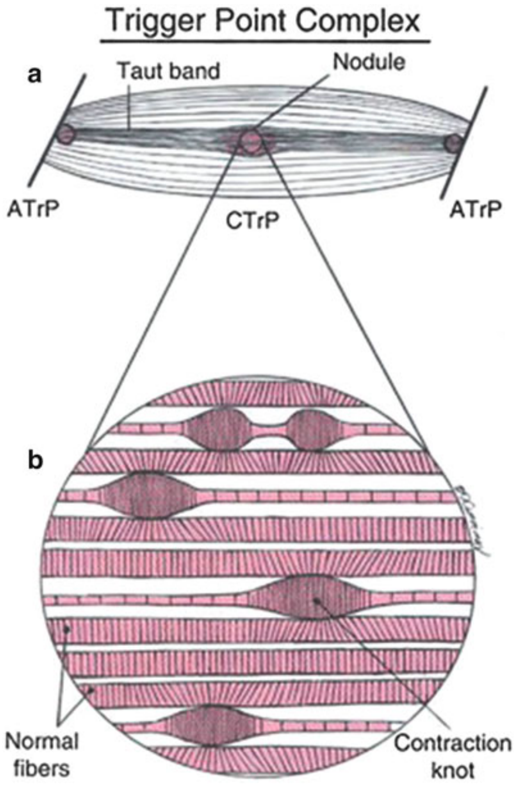

Fig. 3.1 Schematic of a trigger point complex in longitudinal section

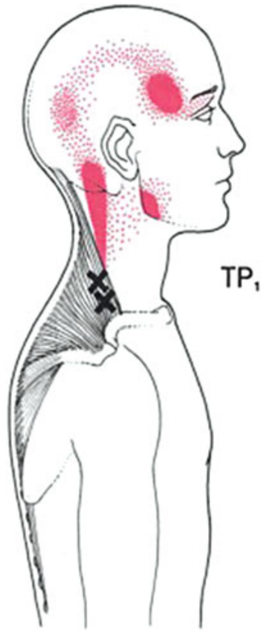

Fig. 3.2 Referred pain pattern and location of (X) of central trigger point 1, identical to GB-21, in the upper trapezius muscle

Table 3.3 Location of fibromyalgia tender points

Localized pain in a taut band of muscle
Local twitch response to cross fiber stimulation of the taut band
Pain to deep palpation that is recognized pain
Referred pain to a characteristic distant region based on myofascial referral maps
Restricted movement in joints related to muscle
Weakness that is not caused by neurological compromise
Autonomic dysfunction

Gerwin et al. [47]

condition and are often an overlooked cause of pain in individuals with coexisting joint or visceral disease, including cervical disc lesions, hip osteoarthritis, temporomandibular joint disorders, pelvic pain, headaches, and epicondylitis [49–53].

Despite the prevalence of MTrPs as a cause of pain, it was not until the 1930s that we began to understand the underlying pathophysiology. John Kellgren was a research assistant under Sir Thomas Lewis at University College Hospital, London, when they initiated a series of investigations on muscle pain by injecting hypertonic saline into healthy volunteer medical students. The students were asked to describe the pain experienced, and it was found that the pain would spread in particular patterns some distance away that they called the zone of pain referral (see Fig. 3.3). Kellgren then described similar zones of pain referral that would occur when pressure was applied to muscle tender spots in patients with “fibrositis” or “myalgia.” He theorized that the pain arose due to nerve hyperactivity, given that he could alleviate

Fig. 3.3 Compensation scoliosis leading to widespread muscle imbalance and strain in the postural muscles

the pain for several days by injecting local anesthetic into the tender nodules [54]. During the 1940s, Janet Travell continued Kellgren's early work and coined the term myofascial trigger point for these hyperirritable tender regions in muscles [46].

Recent evidence suggests that the muscle dysfunction seen in both MPS and FM is due to both a central and peripheral sensitization process. In a study by De Stefano et al. comparing patients diagnosed with FM and MPS with normal healthy controls, biopsy results from the trapezius muscle were stained using anti-substance P sera. The mean optical density (OD) of the immunostaining was found to be significantly higher in the MPS and FM groups compared to controls with the OD of the MPS group also being significantly denser than the FM group [55]. Biopsy results of the deltoid in patients with FM, assaying for messenger RNA (mRNA) of various neuropeptides, have shown that substance P (SP) is not generated in the muscle and so, by inference, must be coming from the small nerve fibers in the muscles [56]. Recently, a group at NIH has developed a 32-gauge microdialysis needle that is capable of collecting small volumes (~0.5 μL), at subnanogram levels of solutes <75 kDa, from muscle tissue in vivo [57]. With this device, the local muscle biochemical milieu in subjects with and without active MTrPs in the upper

trapezius muscle was examined. The main outcome measures were concentration levels of protons (pH), substance P (SP), calcitonin gene-related peptide (CGRP), bradykinin, serotonin, norepinephrine, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), all of which were significantly elevated in the subjects with active MTrP when compared to subjects with latent MTrP or healthy controls. These findings confirm the biopsy results of De Stefano's study and are strongly suggestive that a process of neurogenic inflammation fuels the soft tissue pain found in MPS and FM.

Neurogenic inflammation is evoked by activities of primary afferent sensory fibers or nociceptors (NCs), specifically by Aδ and C-fibers, causing the retrograde release of the neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) into peripheral tissue [58–60]. Any strong stimulation to the central nervous system can lead to the retrograde release of neuropeptides in the periphery via a phenomenon called dorsal root reflexes (DRRs). For example, Peng et al. have demonstrated that stimulation of the periaqueductal gray region (PAG) in the midbrain of mice led to multisegmental activation of the dorsal roots causing retrograde release of neuropeptides in the periphery and neurogenic inflammation. Peng also describes DRRs in response to peripheral nerve stimulation and with inflammatory models of visceral pain, causing a multisegmental spread, above and below the primary root level of input [61]. It has been suggested that SP acts on venules to cause plasma leakage, and CGRP acts on arterioles producing vasodilatation [62, 63]. This role of the NCs may be critical even in a healthy organism as the vasodilatory effects of SP and CGRP can act to balance the vasoconstrictive effects of the sympathetic nervous system [64, 65]. Thus, both antidromic vasodilatation via tonic activity of the NCs and sympathetic vasoconstriction interact with each other to maintain the state of blood perfusion in the skin. This strongly suggests that the muscle NCs are not merely a passive signaling system, designed to record and transmit potentially noxious stimuli centrally, but rather play an active role in the maintenance of normal tissue homeostasis by balancing the vasoconstrictive activity of the sympathetic nervous system and sensing the peripheral biochemical milieu. With tissue injury, the secretion of SP and CGRP increases, leading to vasodilatation, plasma extravasation, localized swelling, and the release of sensitizing substances that can alter the responsiveness of the NC leading to spontaneous pain and a lowered pain threshold [66]. Peng's work highlights that sensitization of the muscle nociceptor may occur in some cases without local tissue injury but can be a manifestation or sign of pathology elsewhere in the body or in the central nervous system itself.

These experimental findings raise the question as to whether the abnormal finding at the active MTrPs is truly local, potentially dependent upon a process of segmental sensitization initiated by some form of local trauma. An alternative explanation is that individuals who develop active MTrPs have a systemic neuroendocrine dysregulation that leads to muscles remote from active or latent MTrPs to have similar biochemical profiles to the MTrP itself. In a recent study, also at NIH, subjects with localized pain related to an active MTrP in the upper trapezius were assessed both at the active MTrP site and at a remote nonpainful site located in the medial gastrocnemius utilizing the same in vivo microdialysis technique [67]. The within-group comparisons

showed that the peak analyte levels in the MTrP of the upper trapezius were significantly higher than the levels in the gastrocnemius in subjects with either an active or latent MTrP, whereas there was no significant difference between the two muscle locations in the healthy controls. Interestingly, the between-group comparisons of the active MTrP group with the latent and healthy control groups demonstrated significantly elevated concentrations of all analytes, with lower pH and higher levels of SP, CGRP, serotonin, bradykinin, and TNF-α in the nonpainful gastrocnemius muscle of the active group. This suggests a systemic process in the active group that is still subthreshold in the gastrocnemius but which has reached levels in the upper trapezius to cause active pain at rest.

Potentially in FM, the process has continued to evolve, either due to environmental or genetic factors or both, where the neurogenic inflammatory process has reached a critical point, causing widespread pain. Theoretically then, in MPS, the nervous system has been able to suppress the systemic release of the irritating neuropeptides sufficiently to keep pain symptoms localized. This would fit the clinical findings that patients with MPS generally are less likely to show evidence of a multisystem sensitization process, with a lower prevalence of some of the associated disorders seen in FM such as irritable bowel syndrome and interstitial cystitis [68].

Time may also play a role in the progression to widespread pain, in that the untreated pain from a localized MTrP may cause sustained abnormal afferent drive to the dorsal horn, which could induce spread of the central sensitization process. In animal models of pain, a nociceptive input from skeletal muscle is much more effective at inducing neuroplastic changes in the spinal cord than input from the skin [69]. Experimentally induced myositis in animal models also leads to segmental spread of the response to second-order neurons in the muscle's receptive field of the dorsal horn. Hoheisel et al. found that in an experimental model of inflammatory muscle pain, the sustained noxious afferent drive from the gastrocsoleus (L5) muscle also activated second-order neurons in the L3 segment. This segment would ordinarily not be activated by noxious stimulation of the gastrocsoleus in noninflamed muscle, suggesting the opening of previously ineffective multisegmental connections [70]. The expansion of the receptive field in the dorsal horn is a result of central sensitization [66]. Sustained noxious afferent drive to the dorsal horn and central nervous system (CNS) can eventually cause sensitization of contralateral segments as well. Pain that spreads contralaterally has been reported in complex regional pain syndrome (CRPS) and other chronic pain conditions [71–73]. There have also been reports of contralateral spread of symptoms after nerve lesions or inflammation in animal models of neuropathic pain [74]. In humans, an intradermal injection of capsaicin leads to the development of contralateral hyperalgesia and allodynia [75]. The contralateral effects of strong noxious input to the CNS have both sensory and motor effects. For example, in a study of patients with chronic, unilateral MPS, bilateral local twitch responses were found in subjects with unilateral needle stimulation of the irritable focus in the upper trapezius [76]. The etiology behind the contralateral spread of pain and motor irritability is largely unknown; however, based on our current understanding, contralateral changes arise via altered spinal processing of incoming sensory information [77–79]. Spinal glia cells and

proinflammatory cytokines have been documented as important factors behind the contralateral spread of symptoms [80]. Given this phenomenon, early and effective treatment of MPS is critical in preventing central sensitization, thereby preventing what begins as a segmental process to evolve into a systemic condition, especially in individuals who may have genetic, endocrinological, and or psychological risk factors for the development of widespread pain.

Treatment and Management

The main difference when considering the treatment options for MPS versus FM is the fact that in MPS, the pain has remained localized to a region of the body and therefore, can potentially benefit from more specific, focal treatments. The most direct treatment of MPS is to use needle stimulation with or without injected substances in the attempt to deactivate or relieve the pain associated with an active trigger point. The work of Shah has provided the first clue from a basic science standpoint that direct needling into an active trigger point has a physiological effect on reducing the concentrations of the irritating substances believed to be central to the pain associated with MTrPs [57]. A systematic review published in 2001 of 23 randomized controlled trials (RCTs) supports the findings of Shah that the nature of the injected substance makes no difference to the outcome of trigger point injections and that there is no therapeutic benefit in wet over dry needling [81]. Subsequent to this review, there have been a number of important studies looking more directly at dry-needling techniques to deactivate an MTrP both from the standard medical literature and the acupuncture literature. These studies support that dry needling into muscle provides therapeutic benefit in a number of pain conditions including myofascial neck, low back, and shoulder pain [82–87]. The majority of these studies compare minimal needling techniques to the use of an acupuncture dry-needling method that relies upon eliciting a local twitch response (LTR) in order to reach a reliable treatment result. This suggests that the pain benefit of needling an MTrP when an LTR is elicited is more than the nonspecific effects of acupuncture analgesia due to the release of endogenous opioids [88].

The relative benefit of dry needling should not suggest that injection of more specific substances into an MTrP may have longer lasting effects than either dry needling or local anesthetic injection. Recently, there has been increasing interest in the use of the 5-HT3 receptor antagonist tropisetron for injection into MTrPs following the demonstration of its efficacy when administered systemically in patients with fibromyalgia [89, 90]. One potential action of this agent may be to prevent SP release from sensory nerves and thereby reduce peripheral sensitization in MTrPs. Botulinum toxin may also have an effect on reducing the release of neuropeptides from sensory neurons [91, 92]. However, the literature on botulinum toxin injection has not demonstrated an effect over and above the needling effect as it has not been shown to offer any advantage over saline or local anesthetic and is significantly more costly to administer [91–95].

There are a variety of noninvasive treatments for MPS that are used. Few if any have substantial support in the literature [96, 97]. Many of these therapies can be included under the general category of physical medicine and rehabilitation techniques which when coordinated in an overall treatment plan may provide some benefit. These include modality-based interventions, manual therapies, conditioning, stretching and strengthening methods, mind-body or relaxation techniques, and postural realignment strategies.

In general, because of the lack of evidence for most passive therapies, including ultrasound and various electrical stimulation therapies, the optimal approach should take into account our current understanding of the underlying mechanism outlined above. This implies that much like the treatment of fibromyalgia, the approach should focus on decreasing those factors that may enhance the noxious afferent drive to the CNS to prevent sensitization spread. The first step is to identify the cause or underlying perpetuating factors. In broad terms, these can be either structural or medical. Structural causes include joint dysfunction or inflammation with common areas involving the facet joints of the spine and the sacroiliac, shoulder, and hip joints. The joint pathology can lead to guarding mechanisms and postural compensation patterns that in a susceptible individual can lead to myofascial dysfunction of the related muscles involved in stabilizing that joint or in accessory muscles that overcompensate for the accompanying dysfunction in the joint. For example, an impingement syndrome of the shoulder can lead the stabilizing muscles, including the rotator cuff, deltoid, and pectoralis muscles, as well as the accessory muscles, including the scalenes, upper and lower trapezius, levator scapulae, and rhomboids, to adopt a pattern of increased tone that can lead to a secondary regional myofascial pain condition. Other postural issues such as a compensation scoliosis due to pelvic obliquities and sacroiliac joint dysfunction can lead multiple muscle groups to develop myofascial dysfunction (see Fig. 3.3).

There are a number of medical factors that have been impugned as perpetuating factors (see Table 3.4), including vitamin B12, iron, and vitamin D deficiency and thyroid disorders [68]. Although B12 deficiency is primarily associated with neurological consequences, the nerve dysfunction and anemia can make patients more prone to myofascial pain [98]. Pernicious anemia is a marker of B12 deficiency. However, because B12 deficiency frequently exists in the absence of anemia, serum B12 concentrations below 300 pg/mL should be treated. Methylmalonic acid and homocysteine levels are good markers for metabolic abnormalities caused by B12 insufficiency [99]. Iron deficiency can cause anemia, fatigue, poor endurance, and muscle pain. Iron stores are assessed best by measuring serum ferritin [100]. In a study on the association of low iron with restless leg syndrome, levels below 25 ng/mL were found in 60% of cases and below 50 ng/mL in 83% of cases studied [101]. This suggests that not only are serum ferritin levels below 20–25 ng/mL clinically significant in restless legs syndrome but that levels below 50 ng/mL are possibly clinically significant and likely to be suboptimal. Perhaps the best evidence for an association with soft tissue pain and nutritional deficits lies with vitamin D deficiency [102, 103]. Vitamin D deficiency is associated with musculoskeletal pain, loss of type II muscle fibers, and proximal muscle atrophy [104]. Values above 20 ng/mL

Table 3.4 Possible laboratory tests and measures

Rheumatological disorder	
Osteoarthritis	Radiographs, rheumatology referral
Rheumatoid arthritis	Rheumatology referral
Endocrine disorder	
Thyroid disorder	TSH
Estrogen status	FSH
Testosterone status	Free testosterone
Growth hormone status	IGF-1
DHEA status	DHEAS
HPA axis status	AM cortisol
Infectious disease	
Lyme disease	Lyme ELISA/Western blot
Hepatitis C	Hepatitis C antibody
HIV infection	HIV screening test
Nutritional status	
B12 deficiency	B12, methylmalonic acid, and homocysteine levels
Vitamin D deficiency	Vitamin D
Iron deficiency	Fe, serum ferritin
Sleep disorder	
Sleep apnea	Sleep study
Narcolepsy	Sleep study
Sleep phase disorder	Sleep study
Psychological disorder	
Depression	Beck depression inventory (BDI)
Anxiety	Beck anxiety inventory (BAI)
Functional status	Fibromyalgia Impact Questionnaire (FIQ)
Autonomic dysfunction	
Postural orthostatic tachycardia syndrome	Tilt table test
Neurally mediated hypotension	Tilt table test
Peripheral pain generators/specific pain conditions	
Disc herniation	MRI spine
Chiari I malformation	MRI foramen magnum
Spinal stenosis	MRI spine
Endometriosis	Gynecology referral
Bowel and bladder dysfunction	
Irritable bowel syndrome	Gastroenterology referral
Irritable bladder syndrome	Urology referral

were considered normal. However, other studies suggest that levels below 34 ng/mL represent vitamin D deficiency [105].

It is generally agreed that overt thyroid disease can lead to diffuse pain complaints and should be treated appropriately. However, the issue becomes more controversial in patients with borderline values who are suggested to have "subtle thyroid dysfunction." Unfortunately, there is little in the literature to guide treatment. There is some evidence that patients with FM are more likely to have thyroid antibodies and be at

risk for thyroiditis [106]. Individuals with post-traumatic stress disorder have been found to have higher levels of circulating antibodies and lower cortisol levels suggesting an altered regulation of the immune system, putting individuals with chronic stress at risk for autoimmune diseases [107]. A more controversial area is impaired conversion of T4 to T3. Conversion of inactive to active thyroid hormone is the result of 5′-deiodination of T4 which occurs in the liver [108]. As a result, some recommend that in patients with soft tissue pain, fatigue, a feeling of being cold, constipation, and dry skin, thyroid supplementation could be beneficial with the goal of bringing the thyroid-stimulating hormone (TSH) levels to below 1.5 units [68].

Chronic infections can lead to diffuse muscular and joint pain, with Lyme disease and hepatitis C being the best known examples [109]. However, parasitic infections including babesiosis and ehrlichiosis as well as mycoplasma infection and enteroviruses can be of concern [68]. It is unknown at this time whether the pain issues that develop in the chronic situation are related to subtle ongoing chronic infection versus an abnormal neuroendocrine and immunological response to the stress of the infection that leads to chronic widespread pain. Interestingly, in the case of chronic Lyme and mycoplasma infections, use of minocycline may actually be working to influence the effects that spinal cord glial cells have on central sensitization and thereby abrogating abnormal pain processing rather than working on a putative ongoing infection [79, 110, 111].

Other Nondrug Therapies

These treatment components can be utilized and recommended to patients at any point in the presentation of symptoms. Education and support groups are among the therapies with moderate to strong efficacy, and they can assist with coping and validation of symptoms. Acupuncture, relaxation therapies, biofeedback, hypnotherapy, massage, and balneotherapy have also demonstrated some benefit in management of FM symptoms [112]. However, many of the studies supporting these treatments suffer methodologically, as they lack adequate control groups. The issue of how to control for the placebo effect in complementary and alternative medical intervention trials is complex and leads to uncertainty about how to interpret the results [113–116]. For example, although the majority of acupuncture studies do show benefit for patients with FM, the 5 trials that included a sham acupuncture control group showed no statistical difference between the verum and sham acupuncture groups [117].

Upon diagnosis of FM or chronic MPS, a stepwise program is recommended based on current evidence that emphasizes the initiation and maintenance of lifestyle changes in the arena of exercise, stress reduction, sleep hygiene, and dietary changes [118, 119]. Aerobic conditioning has been shown to improve function and mood in patients with FM with mixed effects on pain and tender points [120]. Exercise has an independent effect on mood stabilization, but exercise dose was important, only getting significant improvement at levels of exercise with an energy expenditure of 17.5 kcal/kg/week, which may have implications for patients with

Table 3.5 Subgroups of fibromyalgia patients

Cluster 1: "typical FM patient in primary care"	
	Low tenderness
	Moderate depression/anxiety
	Moderate catastrophizing
	Moderate control over pain
Cluster 2: "FM patient in tertiary care"	
	High tenderness
	High depression/anxiety
	High catastrophizing
	Low control for pain
Cluster 3: "FM patient with neurobiologic presentation"	
	High tenderness
	Low depression/anxiety
	Low catastrophizing
	High control over pain

Adapted from [126]

FM given the difficulty many patients have reaching reasonable levels of aerobic fitness when pain becomes a limiting factor [121]. Ideally, exercise has to be gradually increased at a pace that is slower than in the non-FM population but with the goal of reaching an exercise volume of 30–60 min of moderate intensity aerobic exercise at least two to three times a week.

Education and cognitive behavioral therapy can play a role in the treatment of FM. In a study of different self-management strategies for FM, the beneficial effects of exercise were enhanced by having patients go through the Arthritis Foundation Fibromyalgia Self-Help Course [122]. Similarly, cognitive behavioral therapy (CBT), which teaches patients how to better cope with pain and achieve specific functional goals, has been shown to be effective when compared to standard care, but there is poor compliance with strategies over time [123]. In addition, there is evidence to suggest that different approaches to psychological interventions may prove more effective for different patient subsets. For example, in a study comparing CBT versus operant behavioral therapy, the patients that responded best to the operant approach were patients with more pain behavior, catastrophizing beliefs, higher levels of healthcare utilization, and more solicitous spouse behaviors. CBT responders tended to have less pain behavior but higher levels of affective distress, lower coping abilities, and less solicitous spouses [124, 125].

Recent research has delineated clusters of FM patients in order to help identify the most efficacious treatment plan for each patient (see Table 3.5) [126]. Physicians should use the following categorization and stepwise program in determining appropriate evidence-based treatment for the FM patient (see Fig. 3.4). It is important to validate the patient's symptoms and emphasize the nondestructive nature of FM. Patients may be hoping for a "magic pill" or "quick fix"; therefore, education regarding the goal of FM treatment as improved functioning, and not the complete elimination of all symptoms, is vital to avoid unrealistic expectations. It is important to clearly explain all aspects of treatments and stress the significance of the patient's active role in any treatment.

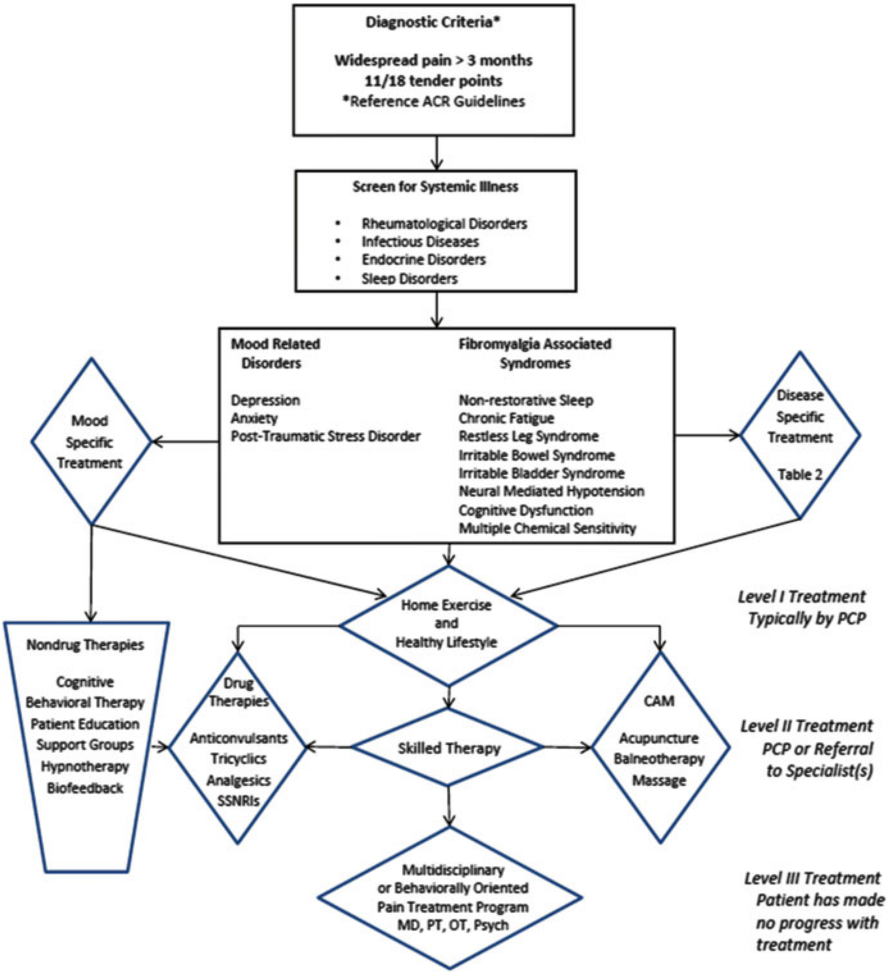

Fig. 3.4 Treatment algorithm for fibromyalgia

Level I Treatment (Patient Education and Lifestyle Changes)

Patient education and lifestyle modification may adequately treat patients who fall into clusters 1 and 2. A healthy lifestyle, including the avoidance of caffeine, eating a healthy diet, regular exercise, stress reduction, and proper sleep hygiene, may control symptoms. In a population survey of 8,572 respondents of whom 12% reported chronic widespread pain (CWP), the women with CWP, compared with those without, reported an unhealthy diet (e.g., fruit/vegetable consumption less than once per week and increased intake of food with a high trans-fatty acid index), and had an elevated body mass index [127]. Exercise is a mandatory component, with the caveat that the patient begins slowly and advances as tolerated. Patients

should be counseled regarding gentle exercise rather than vigorous, jarring body movements. Swimming, walking, and low-impact aerobics are well tolerated. In a study comparing land- and pool-based programs, after 20 weeks, significant improvements were seen in both groups on measures of cardiovascular capacity, walking time, and daytime fatigue; however, the pool-based group showed greater improvements in number of days of feeling good, self-reported physical impairment, pain, anxiety, and depression [128].

There is a growing interest in alternative exercise strategies to manage pain. A recent trial by Wang et al. compared a short form of Tai Chi (10 movements) to a control intervention that consisted of wellness education and stretching. Treatment sessions lasted 60 min and took place twice a week for 12 weeks. The primary outcome was the Fibromyalgia Impact Questionnaire (FIQ) with significant improvements seen at conclusion of the intervention and at 24-week follow-up in the Tai Chi group when compared to the control group, with a change in pre- and post-FIQ scores of 62.9 ± 15.5 and 35.1 ± 18.8, respectively, in the Tai Chi group, versus 68.0 ± 11 and 58.6 ± 17.6, respectively, for the control group ($p<0.001$) [129]. This change was so great (e.g., an improvement of 28.6 points on the Fibromyalgia Impact Questionnaire at 24 weeks), an effect that is unprecedented in fibromyalgia trials of either pharmacologic or nonpharmacologic interventions, that some researchers in the field questioned whether the study was biased by an "irreproducible and intangible mechanism" as the basis of the treatment effect rather than a specific effect of Tai Chi [130].

Level II Treatment (Monitored Pharmacologic Treatment with Skilled Care)

Healthcare providers may consider initiating medications and referrals to monitored or supervised therapies for cluster 3 patients or patients who do not respond to level 1 treatment [10].

Level III Treatment (Multidisciplinary Program)

Patients for whom levels 1 and 2 treatment have failed and some patients in cluster 3 should be referred to a multidisciplinary treatment program [131, 132]. The providers in such centers have familiarity with the treatment of a variety of chronic pain conditions such as fibromyalgia. Typical multidisciplinary teams typically include physicians, psychologists, psychiatrists, nurses, physical therapists, occupational therapists, vocational counselors, social workers, and other specialized healthcare providers. Such programs emphasize structured, goal-based rehabilitation and typically include education, progressive exercise, individual or group cognitive behavioral therapy,

and medical management of pain, fatigue, sleeps disorders, mood, and other symptoms in a coordinated fashion. One study that had 6-month follow-up data on patients who had completed a 4-week interdisciplinary program suggested that patients did maintain gains in pain, life interference, sense of control, affective distress, and depression [133]. Gustafsson showed significant improvement on measures of quality of movement and mood following a 12-week multidisciplinary program that was partially sustained after a year [134]. Sustained improvements in average pain intensity, pain-related disability, depressed mood, days in pain, and hours in pain were found at 15-month follow-up after a 6-week multidisciplinary rehabilitation program. The long-term changes in Pain Disability Index were found to be influenced by exercise adherence and income status [135]. Suman et al. demonstrated sustained benefits in pain scores and aerobic fitness at 1-year follow-up after a 3-week residential multidisciplinary treatment program, supporting that the acquisition of physical exercise as a coping strategy for managing chronic pain may explain the long-term effects of the treatment intervention [136].

Drug Therapies

In FM and MPS, medications are typically geared toward central pain modulation and symptom management and generally require a combination of agents [137]. Pharmacotherapy has been most successful with central nervous system agents, including medications in the classes of antidepressants, muscle relaxants, and anticonvulsants. These medications have effects on various neurochemicals (e.g., serotonin, norepinephrine, substance P), which in turn affect activity in the brain and spinal cord, including modulation of pain sensation and tolerance. Medications with moderate to strong efficacy for the treatment and management of FM syndrome are summarized in Table 3.6.

Tricyclic antidepressants have shown to be of benefit in FM with the strongest effects on sleep and more modest effects on relieving pain [138]. In some studies, cyclobenzaprine has been found to be as effective as amitriptyline [139, 140]. Other antidepressant medications, such as the selective serotonin reuptake inhibitor (SSRI), including paroxetine, citalopram, and fluoxetine, have shown inconsistent effects in FM [1]. Adding a second antidepressant or medication is often necessary [141]. However, in a placebo-controlled 12-week study of fluoxetine in FM, patients had significantly improved mood, sleep, and pain when compared to the control group [142]. Selective norepinephrine reuptake inhibitors (SNRIs) have the added benefit of raising both serotonin and norepinephrine levels, thereby having a stronger influence on the descending pain modulatory system. Several of these agents have demonstrated efficacy with FM patients. Venlafaxine at low doses acts primarily as an SSRI and at higher doses, in the 300 milligrams per day (mg/day) range, also engages norepinephrine reuptake inhibition [143]. For example, there was no improvement in pain scores in a randomized controlled study of a low fixed dose of venlafaxine (75 mg/day) in FM patients, but in an open-label, flexible-dose study,

Table 3.6 Medications for fibromyalgia syndrome

Tricyclic antidepressants[a]	
Amitriptyline 25–50 mg at bedtime	
Cyclobenzaprine 10–30 mg at bedtime	
Analgesics[b]	
Tramadol with or without acetaminophen 200–300 mg/day	
SSRIs[b]	
Fluoxetine 20–80 mg with or without tricyclic at bedtime	
SNRIs[b]	
Venlafaxine 150–300 mg/day	
Milnacipran 50–100 mg bid	
Duloxetine 60 mg qd to bid	
Anticonvulsants[b]	
Gabapentin 1,200–2,400 mg/day	
Pregabalin 300–450 mg/day	

Adapted from [10]
[a]Strong evidence for efficacy
[b]Modest evidence for efficacy

where the average dose was 167 mg/day, significant improvement was seen in pain and other FM symptoms [143, 144]. At this dose, there can be an increased risk for hypertension, but there has been no evidence of significant alterations in electrocardiogram (ECG) parameters including PR, QT, QRSD, and QTc interval [145] [146]. Another SNRI, duloxetine has now been approved by the US Food and Drug Administration (FDA) for the treatment of adults with major depression, general anxiety disorder, painful diabetic peripheral neuropathy, and symptoms related to fibromyalgia. As of November of 2010, it has also been approved by the FDA for treatment of chronic musculoskeletal pain and chronic low back pain and pain due to arthritis. Unlike venlafaxine, duloxetine acts both on the serotonin and norepinephrine reuptake inhibition throughout its dose range. Large randomized controlled studies have shown that duloxetine at 60 and 120 mg/day provides significant benefit over placebo on outcomes of pain, mood, fatigue, function, and measures of quality of life [1]. However, there has been concern about the clinical relevance of the results of these studies [146]. Duloxetine has a better cardiovascular safety profile compared to venlafaxine at therapeutic doses, but because it is metabolized by the liver P450 system, it is strongly influenced by other drugs that inhibit the CYP1A2 and CYP2D6 enzymatic system, and drug levels can rapidly increase when coadministered with other antidepressant agents such as paroxetine, fluoxetine, and fluvoxamine as well as quinidine [147]. Milnacipran has been available in Europe since 1997 for depression and received FDA approval for fibromyalgia in 2009. Like duloxetine, it has a dual effect on serotonin and norepinephrine reuptake inhibition throughout its normal dose range. There is also some evidence that milnacipran has a modest effect on inhibiting the N-methyl-D-aspartate (NMDA) receptor, which is strongly implicated in central sensitization [148]. A dose of 50–100 mg taken twice a day has been shown to have a significant effect on reducing pain and improving measures of quality of life and function in patients with FM [1]. Because

milnacipran is not metabolized and does not influence the hepatic cytochrome P450 system, it has a greater safety profile when administered with other antidepressants or drugs [147]. A recent meta-analysis of the effect of amitriptyline, duloxetine, and milnacipran on pain related to FM suggests that amitriptyline is superior to the newer agents, with superior efficacy in achieving at least a 30% pain reduction, although the studies on amitriptyline had more methodological flaws with shorter follow-up periods. In contrast to duloxetine and milnacipran, amitriptyline also had greater benefit on sleep and fatigue measures but was inferior when assessing mood, in part, because low doses were used in the FM studies [146]. Nevertheless, use of the tricyclic antidepressants poses certain risks with potential cardiac toxicity and other safety issues related to their anticholinergic and antihistaminergic effects [149].

Given the growing recognition that the symptoms related to FM are due to a central sensitization disorder, there have been a number of recent large randomized trials using the anticonvulsants pregabalin and gabapentin, both of which are believed to influence pain via their binding to the alpha-2-delta protein which is a subunit of voltage-dependent calcium channels [150]. Pregabalin has been FDA approved for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and for the management of FM. The randomized controlled studies of both pregabalin and gabapentin have shown significant improvement in pain, sleep, function, and quality of life measures. The dose ranges for pregabalin was from 150 to 300 mg twice a day and for gabapentin 1,200–2,400 mg/day. Limiting side effects include fatigue and other cognitive impairments as well as peripheral edema and weight gain. Potentially, other anticonvulsants could have an effect on reducing central sensitization and pain modulation in FM; however, there have not been sufficient studies to make strong recommendations.

Tramadol, taken with or without acetaminophen, has demonstrated efficacy in reducing pain in four randomized, controlled trials of FM patients [151–153]. The analgesic effect of tramadol is in part due to its weak affinity for the mu-opioid receptor, but in addition, there is a central pain modulatory effect through serotonin and norepinephrine reuptake inhibition [154]. NSAIDs may be useful for pain relief when combined with TCAs, although there is no evidence that these drugs are effective when used alone [155]. Corticosteroids have not proven to be effective for the management of FM [156]. The issue of whether opioids could benefit patients with FM is controversial. However, the best evidence that we have now is that opioids are ineffective for FM-related pain. In a study comparing the immediate effect on pain, tender points, and exercise tolerance after the intravenous administration of lidocaine, ketamine, or morphine in a randomized and blinded fashion, it was found that morphine had no effect on any of the measured outcomes. Only ketamine, a potent NMDA receptor antagonist, reduced pain scores and tender point sensitivity and improved exercise tolerance [157]. In addition, there is a concern that prolonged exposure to opioids can cause central sensitization or opioid-induced hyperalgesia and so could, theoretically, exacerbate a process such as FM that is already thought to be due to altered central pain processing [158, 159].

Another area of controversy is the use of the hypnotics and sedatives for sleep restoration. In a survey of FM in the general population, hydrocodone preparations,

alprazolam, oxycodone preparations, zolpidem, cyclobenzaprine, and clonazepam were perceived to be the most effective agents for sleep [160]. Zolpidem and zopiclone have been found to improve sleep in FM but had no effect on pain [161, 162]. There is one well-controlled trial looking at the benzodiazepines where there was no benefit found [163]. A recent 8-week study using a substance with extremely high abuse potential, sodium oxybate, which is the sodium salt of □-hydroxybutyrate (GHB), a date rape drug, did find significant benefit on measures of pain, sleep, and function [164].

FM patients may be taking many other medications with the potential for adverse interactions and are often more sensitive to side effects. Some antidepressants lower the seizure threshold and, when combined with other agents, such as tramadol, could lower this threshold further. SSRIs may cause drug interactions because of their inhibition of the cytochrome P-450 system. Since the cardiovascular effects of tricyclic antidepressants include postural hypotension, FM patients with dysautonomia, hypotension, and cardiac disease, including cardiac conduction abnormalities or arrhythmias, should avoid the use of these drugs. An ECG is indicated to rule out prolonged QT interval or other rhythm abnormalities in any patient for whom there is concern of beginning a tricyclic antidepressant. They should also be used with caution in patients with hepatic dysfunction.

There is currently little clinical evidence for the use of a variety of commonly used agents – including melatonin, calcitonin, thyroid hormone, guaifenesin, dehydroepiandrosterone, and S-adenosyl-L-methionine – for the treatment of FM. There is some evidence that magnesium (Mg) and other trace minerals may be low in patients with FM. In a study of 32 subjects with the diagnosis of FM, significantly lower serum levels of Zinc (Zn) and Mg were found when compared to age- and sex-matched healthy controls [165]. From a physiological basis, the potential benefit for the use of Mg in patients with FM and other pain conditions, where central sensitization plays a role, is compelling. Magnesium is known to act to reduce catecholamine release during stress, has membrane-stabilizing effects, and has antinociceptive effects by blocking NMDA receptors [166]. Both Zn and Mg have been shown to block NMDA receptor activity acting as allosteric modulators of the NMDA receptor [167]. This suggests that supplementation with Zn and/or Mg could be of benefit to patients with FM. In the case of magnesium, gastrointestinal absorption may limit efficacy. For example, a randomized controlled study of magnesium malate for patients with FM, which had 50 mg of magnesium with 200 mg of malic acid per tablet, found no benefit over a 4-week period when taking six tablets a day or 300 mg of magnesium per day. The trial was then extended during an open-label period for 6 months with dose titration, and then reductions were seen on measures of pain and tender point sensitivity at doses in the range of 600 mg/day [168].

Case 1

A 41-year-old woman presented to her primary care doctor complaining of frequent headaches, fatigue, and diffuse body pain. She reported muscle tightness throughout

her body and constantly feeling "wiped out." Symptoms worsened premenstrually. The patient reported feeling well until approximately a year ago when she developed a "flu-like illness" that included lymph node swelling, fatigue, aching, and sore throat. Her acute respiratory symptoms lingered for several weeks. When they resolved, the patient was left with continued diffuse myalgia pain. Since that time, she has experienced chronic sinus congestion, generalized aching, stiffness, digestive problems, and fatigue. The patient noted daytime fatigue, difficulty with early and middle-of-the-night insomnia, anhedonia, anergia, low libido, as well as difficulty with concentration, attention, and memory. She has been married for 10 years and has two children. She worked as an elementary school teacher until last year when she quit because of increasing work stress over the previous 3 years. The patient had hoped that with this change, her fatigue and pain symptoms might have resolved, but they did not, prompting her to seek medical advice.

Medication History

The patient managed her pain symptoms with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDS) or headache medications. She uses a nasal steroid spray for allergies, a low-dose combined oral contraceptive, and a multivitamin daily.

Medical History

The patient's past medical history included migraine headache without aura since adolescence, two healthy pregnancies, and multiple environmental allergies. She underwent a cholecystectomy in the past year. She has no prior history of depression or other mood disorders.

Family History

This patient's mother has a history of migraine headache, obesity, and rheumatoid arthritis. Her father has a history of alcoholism and depression.

Review of Systems

The patient denied any numbness in the hands or feet but reported that they are usually cold. She denied fever, chills, unexplained weight loss, and bowel or bladder incontinence but noted frequent alternations between constipation and diarrhea. She denied cardiac, pulmonary, endocrine, ear, nose, or throat problems other than

dry eyes, occasional heart palpitations, frequent dizziness, and chronic sinus and nasal stuffiness. She has multiple environmental allergies. She reported bloating, urinary frequency, dysmenorrhea, and loss of sexual interest. She is a lifetime non-smoker and drinks 1 glass of wine with dinner. She consumes several caffeinated beverages during the day to stay alert. She does not exercise, has a poor diet, and has gained 20 pounds over the past 3 years.

Examination

The patient is an adult woman with a weight of 152 pounds and a height of 5 ft 4 in. She had slight internal rotation in her shoulders and a forward thrust of her head. She had increased muscle tension in her neck and shoulder regions, with some trigger points and 14/18 tender points consistent with fibromyalgia (FM). The remainder of the complete physical examination was normal; she has no rashes and no gross joint swelling, redness, or heat and had full range of motion in all joints tested.

Workup

Given the patient's history of weight gain, fatigue, temperature regulation problems, and mood changes, the clinical workup included a thyroid function test, vitamin D levels, B12 levels, and a complete blood count. In many cases, obtaining erythrocyte sedimentation rate, rheumatoid factor, creatine kinase, antinuclear antibody, and calcium levels can screen out a number of systemic illnesses of concern. However, other rheumatologic testing was not done, given the lack of historic and physical findings to suggest an inflammatory rheumatic disease. A Lyme titer was ordered because of the history of a viral illness at onset of the symptoms. Finally, because of the history of palpitations and the plan to start a tricyclic antidepressant (TCA) for improving sleep and helping pain management, an electrocardiogram was ordered to ensure that the patient did not have a prolonged QT interval, which would be a contraindication for the initiation of a TCA. All tests ordered in this case yielded results within normal limit except a vitamin D level of 23 ng/cc and a vitamin B12 level of 250 pg/mL with no evidence of overt anemia.

Diagnostic Considerations

Based on the information above, FM was diagnosed. Evidence in support of FM are:

- Widespread pain lasting more than 3 months
- Fourteen out of 18 tender points present in bilateral locations and in both the upper and lower body

- The presence of recognized associated symptoms including irritable bowel and bladder, dysmenorrhea, nonrestorative sleep, and daytime fatigue
- The absence of any other systemic illness to explain the patient's symptoms

Treatment

The patient was started on 10 mg of amitriptyline and titrated up to 30 mg over a 4-week period. With this, she did have improved sleep and pain; however, due to unwanted weight gain on the amitriptyline, the decision was made to convert to duloxetine, initially at 20 mg a day and then titrated up to 60 mg over a 6-week period. The patient was referred to physical therapy (PT) where the patient was given postural education and a program of muscle strengthening and gentle aerobics was initiated. As she progressed her exercise program, she began to have difficulties with increased pain in her buttocks and hips, particularly on the right side. She was found to have sacroiliac joint dysfunction and myofascial pain of her hip rotators, and her PT program was modified to focus on correcting the joint dysfunction and focusing more on core stabilization exercises. During this time frame, she had a trigger point injection of her right gluteus maximus and piriformis to accelerate her progress in PT. The patient was encouraged to join a gym to continue to progress her exercise at conclusion of the PT. Dietary recommendations were made to reduce her daily intake of sugar, reduce her overall calorie intake to 1,200–1,400/day, reduce her alcohol intake, eliminate dairy to help with her irritable bowel symptoms, and initiate a combination of B-complex vitamins, vitamin D 1,000 IU per day, magnesium malate 400 mg twice a day, and fish oil 1,500 mg twice a day. By the end of 6 months, she was exercising regularly, her sleep was dramatically improved, and her functional bowel issue was less pervasive. Her weight was down to 140 pounds, and she wanted to reduce or stop the duloxetine. The dose was cut in half and she continued to do well. She did continue to have increased pain, especially pelvic pain with her menses. For this, she was referred to a local acupuncturist, which she found extremely helpful. After another 6 months, she was able to titrate off the duloxetine all together while continuing with acupuncture treatments monthly. She also continued to exercise at least three times a week and her weight was down to 130 pounds. Repeat blood tests of vitamins D and B12 showed normalization of her levels.

Case 2

The patient is an 82-year-old gentleman with a history of diabetes, peripheral neuropathy, coronary artery disease (CAD), lumbar spondylosis, and knee osteoarthritis (OA) who is status post a left total knee replacement (TKR) in November of 2010. He has had a long-standing problem in the posterior aspect of his left knee that he describes as if there is a tight rubber band-like feeling that is painful with

standing, walking, and sitting. The pain had been attributed to the knee OA but has continued despite TKR. He was treated by a spine specialist with a trial of lumbar epidural steroid injection without benefit. He has remained active, working out every day at the gym with a stretching program and conditioning routine, but this only seems to aggravate the problem. The pain is localized without radiation below the knee. He does, however, have a peripheral neuropathy caused by the diabetes. In addition, he reports episodes of severe spasm in his left hamstring at night.

Current Medications

The patient takes furosemide, omeprazole, atenolol, irbesartan, glipizide, simvastatin, levothyroxine, aspirin, and calcium, vitamin D, niacin, and omega-3 fatty acid supplements.

Review of Systems

The patient's review of systems was negative except for numbness in both feet that had been long standing. No focal weakness or bowel or bladder issues.

Examination

On standing, there was no evidence of scoliosis or pelvic obliquity. On palpation there was no tenderness over the lumbar facets, facet loading negative, non-tender over SI joint. Forward flexion of the lumbar spine is 50° with extremely tight hamstrings, left worse than right. The patient is able to toe walk, heel walk, squat, and rise up without weakness. Internal/external rotation of the hip is not painful. On neurologic examination, manual motor testing is 5/5 throughout with normal tone. Sensation showed decreased pinprick in feet in stocking glove pattern, normal vibration. Reflexes are 1 out of 4 at right knee, absent left knee, and bilateral ankles with no clonus, toes down going. Examination of the knees revealed no evidence of redness, heat, effusion, or instability. Left knee extension was full but with resistance due to hamstring tightness, right knee extension was full without hamstring restriction. Myofascial exam reveals evidence of a taut irritable band in the left hamstring, palpation of which, reproduces his pain.

Workup

Lumbar MRI revealed a mild disc bulge without stenosis at L1/2 and a diffuse disc bulge with facet and ligamentous hypertrophy with mild to moderate stenosis of the

central canal and lateral recess at L2/3. At L3/4, there is a mild diffuse disc bulge with superimposed left larger than right paramedian and foraminal disc herniations which cause compression of the left L4 nerve root in the lateral recess. At L4/5, there is mild spondylolisthesis with a disc bulge and facet and ligamentous hypertrophy causing mild to moderate spinal and foraminal stenosis. At L5/S1, there is a disc bulge with disc space osteophytes and facet hypertrophy without clear stenosis.

Diagnostic Considerations

Based on the information above, myofascial pain syndrome of the left hamstring was diagnosed. Evidence in support of myofascial pain includes:

- Examination findings of a palpable taut band that reproduces his pain on palpation
- Lack of response to lumbar epidural steroid injections
- Normal hip exam and recent knee replacement that did not improve pain symptoms

Treatment

The patient underwent a course of trigger point injections injecting approximately 3 mL of 1% lidocaine after a local twitch response was obtained in the bicep femoris and semitendinosus muscles of the hamstring. He underwent a series of three sessions performed 3 weeks apart. The patient was encouraged to stretch the hamstring, calves, and hip rotators twice daily using yoga techniques. His pain completely resolved.

Conclusions

Fibromyalgia is a chronic condition characterized by widespread pain with multiple tender points, fatigue, sleep disturbances, mood disorders, and clinically significant functional impairments. Patients with FM pose a challenge to healthcare practitioners because the condition affects multiple aspects of physical as well as psychological functioning. Upon diagnosis, a stepwise program of evidence-based treatments is recommended. Empirically supported treatments include a combination of healthy lifestyle modifications, medication, physical therapy, and psychological treatment for the optimal outcome. The healthcare provider plays a vital role in educating the patient about FM. It is important to validate the patient's experience while emphasizing the nondestructive nature of FM. Healthcare providers should be very clear with patients that the ultimate goal is an improvement in quality of life and level of

functioning, not the total elimination of pain. However, they can reassure patients that there is evidence showing that these goals are realistic and achievable based on the collaboration and active participation of the primary healthcare provider, allied FM specialists, and the patient.

Myofascial pain is a common cause of neuromusculoskeletal pain and dysfunction and, as in the case of fibromyalgia, is often discounted or missed because of the lack of objective imaging or testing to make the diagnosis. There is a growing body of basic science evidence that the muscle dysfunction seen in MPS is due to segmental sensitization. This supports the treatment concept that discovering and eliminating perpetuating factors that may be driving the central nervous system are as important as the local treatment of the active trigger point. Active myofascial trigger points function as dynamic foci of peripheral nociception that can initiate, accentuate, and maintain central sensitization and chronic pain states and may, if left untreated in a susceptible individual, metastasize over time and lead to widespread pain.

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Chapter 4
Gynecologic Etiologies of Chronic Pelvic Pain

Aaron K. Styer

Introduction

Definition

Chronic pelvic pain (CPP) is a common diagnostic and management dilemma which spans a wide diversity of clinical settings. One of the most significant challenges in the diagnosis and treatment of this disorder lies in a lack of consensus for diagnostic criteria. Although there is no gold standard definition, most diagnostic criteria for any pain disorder such as this are predicated on the duration (chronicity), location, and severity of symptoms. In gynecologic publications, the majority of authors have used duration of 6 months or more as the major diagnostic criterion for the definition of chronicity [1]. Despite general agreement regarding chronicity, some controversy exists with regard to temporal characteristics of symptoms. Many have debated whether acceptable symptoms for the diagnosis of CPP should include cyclic (e.g., dysmenorrhea associated with menses or pain during a particular phase of the menstrual cycle), intermittent (e.g., dyspareunia), or noncyclic pain (unpredictable onset). There is also disagreement of what constitutes the "pelvic" location of symptoms. Although CPP has been traditionally considered to be a process of the peritoneal and lower abdominal viscera below the umbilicus and within the boundaries of the anatomic pelvis, some authors have also included portions of the external genitalia (vulva, vagina) and musculoskeletal system (e.g., sacroiliac joint) in close proximity to the bony pelvis.

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Despite variable opinions of what constitutes this disorder, a widely accepted definition for CPP is noncyclic pain of a duration of at least 6 months, which is localized primarily in the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks, which is severe enough to cause functional disability requiring medical evaluation [1, 2]. As mentioned previously, there are many factors which make this disorder a diagnostic challenge. One central factor, pain, is always subjective and is defined as an unpleasant sensory and emotional experience associated with actual and potential tissue damage [1, 3]. Because of the subjective nature of pain, a normal physical examination does not preclude the significance of a patient's pain symptoms or eliminate the possibility of CPP during the initial presentation.

Prevalence and Impact

CPP is a major area of interest in women's health care and is estimated to have a prevalence of 3.8% in woman aged 15–73, similar to that of asthma (3.7%) and back pain (4.1%) [4]. In primary care practices, it is estimated that 39% of women have complained of pelvic pain on at least one occasion [5]. It accounts for approximately 10% of all ambulatory referrals to gynecologists [6]. There do not seem to be any specific demographic factors, such as age, race and ethnicity, education, and socioeconomic status, which are consistently different between women with and without chronic pelvic pain [1, 7, 8]. One group of investigators found that women with CPP were slightly more likely to be divorced or separated [7]. Although CPP is a common disorder of predominately reproductive-aged women and is estimated to occur in approximately 15% of this population, age does not seem to be a specific risk factor [2]. To this end, many investigators have reported the development of CPP in women at all ages [5–7, 9–11]. As will be covered later in this chapter, specific etiologies may be more common particular age ranges [1, 7]. Notably, there is a more consistent association of physical and sexual abuse with several chronic pain disorders in the literature [12]. Approximately 40–50% of women with CPP have a history of abuse (physical and sexual), while many women with a history of sexual abuse tend to have an increased risk for high somatization scores and an increased likelihood for nonsomatic pelvic pain [12–14].

The widespread prevalence of CPP accounts for significant expenditures within the medical system. In the United States (USA), it is the primary indication for approximately 40% of all gynecologic diagnostic laparoscopies and accounts for 12% of the nearly 600,000 hysterectomies performed annually [9–11]. Domestic direct costs for health-care delivery for CPP are estimated to be $880 million dollars per year, while the sum of direct and indirect costs may well be over 2 billion dollars annually [2, 7]. In addition to the obvious monetary costs of this pain disorder, there are many expenditures and losses which are not measured. In particular, many affected individuals with CPP may endure several years of professional and social difficulties including long-term disability, loss of employment, marital discord, and many years of frustration with medical providers [2].

Etiology

The differential diagnosis for the most common disease processes associated with CPP includes visceral sources such as gynecologic, genitourinary, and gastrointestinal systems (Table 4.1). Somatic sources include the pelvic musculoskeletal

Table 4.1 Conditions associated with chronic pelvic pain

Gynecologic	Endometriosis[a]
	Uterine leiomyomata (fibroids)[b]
	Adenomyosis[b]
	Pelvic adhesive disease[b]
	Pelvic congestion syndrome
	Chronic pelvic inflammatory disease[a]
	Ovarian remnant syndrome[a]
	Tuberculous salpingitis[a]
	Gynecologic malignancy[a]
	Prolapse of pelvic contents through vaginal cuff (e.g., fallopian tube, omentum, small or large bowel) following total hysterectomy
	Adnexal cysts
	Cervical stenosis
Nongynecologic	Interstitial cystitis[a]
Urological	Urethral diverticulum
	Bladder neoplasm
	Recurrent urinary tract infection
	Urethritis
	Renal or bladder calculi (nephrolithiasis/urolithiasis)
Gastrointestinal	Irritable bowel syndrome[a]
	Inflammatory bowel disease
	Diverticulitis
	Colitis (of any etiology)
	Colon neoplasm
	Celiac sprue
	Constipation
Musculoskeletal	Myofascial syndrome (trigger points)[a]
	Pelvic floor dysfunction[a]
	Hernia (ventral, inguinal, femoral, spigelian)
	Spondylosis
	Fibromyalgia
Neurological	Herniated disk
	Neuropathic pain
	Fibromyalgia
	Neuralgia (e.g., iliohypogastric, ilioinguinal, genitofemoral, pudendal nerves)[a]
Psychosocial	Prior or current physical or sexual abuse
	Depression
	Somatization disorder
	Substance abuse

[a]Consistent scientific evidence exists to establish causal relationship to chronic pelvic pain
[b]Causal relationship to chronic pelvic pain based upon expert opinion

system and fascia as well as more subtle origins resulting from psychiatric and neurologic disorders (central and peripheral) (Table 4.1) [1]. Given the wide diversity of anatomic and functional organs systems involved in CPP, the primary etiology may not be apparent for many years. Ironically, few, if any, diseases thought to cause CPP meet traditional epidemiological criteria for causality [1]. Reliable evidence suggests that several of the most common symptoms in women with CPP are most likely causal, as in the case of endometriosis, interstitial cystitis, and irritable bowel syndrome [1, 2]. However, many of the diseases listed as causes of CPP are supported only by limited evidence and expert opinion to establish an etiologic relationship [1].

The proportion of women with CPP with sole primary disorders and secondary associated disease process is quite variable and remains uncertain. More often, the symptoms of CPP are associated with several diagnoses and other contributory factors necessitating further evaluation and possible treatment [2]. In a large-scale US study, investigators reported that approximately 25–50% of women seeking medical attention for CPP in primary care practices have more than one diagnosis [4, 8, 15]. For example, endometriosis, irritable bowel syndrome, poor posture, and emotional stress may all contribute to CPP in an individual patient [2]. Although many clinicians may assume that there is a primary gynecologic source of symptoms when a woman presents with CPP, this may not always be a correct assumption. Interestingly, a retrospective analysis of a primary care database from the United Kingdom found that genitourinary and gastrointestinal etiologies were more common than gynecologic diagnoses (e.g., 30.8% genitourinary, 37.7% gastrointestinal, and 20.2% gynecologic) [15].

Women with multiple diagnoses involving more than one organ or anatomic system may usually complain of the greatest intensity of pain compared to those with a single diagnosis or a sole involved organ system. In the previously mentioned British database study, 43% of patients with CPP without gastrointestinal or urological symptoms had moderate to severe pain [15]. In contrast, 71% of women with CPP and both gastrointestinal and urological symptoms had moderate to severe pain [1, 15]. Women with CPP and multisystem symptoms may have more consistent symptomatology than the general population with regard to the prevalence of dysmenorrhea (81% vs. 58%) and dyspareunia (41% vs. 14%) [15].

The exact mechanism by which some disorders cause pain in some women and not in others is unknown. Because of the diagnostic complexity of the multiple etiologies of CPP, an accurate diagnostic approach cannot always be assumed. This is especially true if medical and/or surgical therapy results in a small improvement or no beneficial effects at all. Furthermore, several levels of therapy may be instituted for many years without success prior to definitive confirmation of the true cause of the CPP disorder. In some situations, the exact cause of symptoms may never be discovered despite consultation with several providers in different disciplines. Ultimately, during the diagnostic approach of the CPP patient, and within the scope of this chapter, it is useful to classify etiologies of CPP into either gynecologic or nongynecologic categories. With this system of classification for CPP in clinical

practice, both the primary care physician and gynecologist may diagnose and treat gynecologic as well as nongynecologic causes of this common disorder. Because of the many nongynecologic conditions which may cause CPP, a multidisciplinary approach may be required for comprehensive evaluation and management.

Diagnostic Approach

As with any medical condition(s), obtaining a comprehensive history and developing a thoughtful differential diagnosis is crucial to accurate diagnosis and individualized therapy. This is especially important in the case of CPP due to the significant overlap of the signs and symptoms of many gynecologic and nongynecologic etiologies. Prior to formal interaction with the patient, a particularly effective tool for initial assessment is a pain questionnaire. In many cases, this may serve primarily as a supplement to the history obtained during the patient interview.

Perhaps the most crucial portion of the patient visit is the physical examination. The examination provides the opportunity for the clinician to correlate the details of symptoms gathered during the history to a focused investigation and discovery of physical signs. Ideally, this may provide a more definitive understanding of the underlying cause(s) of CPP. A frequently overlooked facet of the physical examination is the obligation to relay sensitivity to the acute and chronic levels of pain which the patient may have been enduring for several years. Specifically, the "routine" abdominal and pelvic examinations may exacerbate anxiety and emotional stress for many women with CPP [2]. In support of these principles, a slow, careful, and deliberate approach during the examination is preferable in order to minimize patient discomfort. This approach may also allow the patient to remember aspects of the history which she omitted previously, and relate these historical facts to real-time physical findings during the physical examination.

History

In the evolving world of medical care, where less time is allotted to each new patient visit, the pelvic pain intake questionnaire may serve as the initial foundation of the medical history and facilitate this portion of the visit. This document best serves as a supplement to the history obtained during the patient interview and is not meant to be a substitute for the patient's account of her history. Although there are many pain questionnaires available, there is no gold standard. A particularly useful and comprehensive form from the International Pelvic Pain Society may be accessed free of charge by patient and clinician online [http://www.pelvicpain.org/pdf/FRM Pain Questionnaire.pdf.]. This form is noteworthy since it comprehensively covers several facets of gynecologic and nongynecologic symptoms and history, assesses

prior and current history of physical and sexual abuse, and allows the patient to characterize their perception of daily disability from reported symptoms.

The most important endpoint of any medical history is the establishment of a comprehensive and detailed differential diagnosis prior to the physical examination. At a minimum, the history should seek to identify the location, severity, quality, and timing of symptoms. Essential portions of a complete history include:

- Past gynecologic history
  Many benign gynecologic disorders may significantly contribute to symptoms. The most common etiologies include endometriosis, uterine fibroids, adenomyosis, pelvic adhesive disease, pelvic congestion syndrome, and chronic pelvic inflammatory disease. A thorough gynecologic history will provide a solid foundation for the differential diagnosis. This portion of the history includes assessment of when menarche occurred and inquiry of any cyclic or noncyclic pain from the onset of the first menses to the present time. Additionally, any change in frequency, onset, severity, character, and location of pain should be assessed. Of particular interest in the gynecologic history would include any prior history of symptomatic sexually transmitted diseases, pelvic infections, or prior surgical procedures such as a loop electrical excision procedure (LEEP), cervical cryosurgery, or cold knife cone which may raise suspicion for an increased risk for known or unknown pelvic inflammatory disease as potential cause of chronic pain. Other facets of the history, which may assist in formulating the differential diagnosis, include assessment of long-term dyspareunia (e.g., endometriosis, pelvic adhesive disease, pelvic floor dysfunction, interstitial cystitis), exacerbation of baseline constant pain by the onset of menses (e.g., endometriosis, adenomyosis, pelvic congestion syndrome, pelvic adhesive disease), purulent or malodorous vaginal discharge (pelvic inflammatory disease), or pelvic pressure and bloating outside of menses (e.g., uterine fibroids, endometriosis, occult malignancy).
- Past obstetrical history
  The processes of pregnancy and childbirth are traumatic events for the musculoskeletal system and may cause unrecognized damage to the back and pelvis leading to CPP. Specific peripartum risk factors for CPP may include lumbar lordosis, muscle weakness or poor conditioning during the prior pregnancy, delivery of a large infant, significant shoulder dystocia resulting in pelvic trauma (e.g., separation of pubic symphysis), vacuum- or forceps-assisted delivery, and the use of gynecologic stirrups during the delivery [16].
- Past surgical history
  Assessment for any prior abdominopelvic surgery is obviously a pertinent portion of the history for the clinician to obtain. Notably, the surgical history may also be pertinent other than for the diagnosis for which the surgery was performed [1]. For example, chronic pelvic pain has been described following the spillage of gallstones during cholecystectomy [17]. In earlier years, surgical procedures for urinary incontinence (e.g., Burch and Marshall-Marchetti-Krantz procedures) have been reported as a cause of CPP localized to the pubic symphysis

due to osteomyelitis or osteitis pubis [18]. Prior cervical surgery such as the cold knife cone and LEEP has been associated with cervical stenosis, hematometra, and endometriosis [19]. Ironically, some women who have undergone gynecologic or obstetrical surgery prior to the onset of any pain may also be at risk for CPP following specific procedures. Specifically, investigators have reported that 3–9% of women without any preoperative pain may develop pelvic pain or back pain within 2 years of hysterectomy [20]. Cesarean section has also been observed as a risk factor for CPP [21].

Prior laparoscopic or open procedures for removal of uterine fibroids, endometriosis, or ovarian cysts may increase suspicion for either recurrence of disease or for pelvic adhesive disease. If the patient is unsure of the details of a prior procedure or she is not an accurate historian, it is prudent to request operative notes from prior surgeries to confirm the nature and extent of the prior procedure(s) performed.

- Duration of pain
  An understanding of the length of symptoms is necessary to differentiate between acute and chronic processes. As mentioned previously, there is no consensus for the definition of CPP. However, the majority of experts concur that this disorder be present for a minimum of 6 months' duration in order to be considered a chronic process. An accurate determination of the chronicity of symptoms will efficiently guide the initial diagnostic approach and formulation of the differential diagnosis.
- Location of pain
  As mentioned previously, the appropriate location(s) to consider for CPP is the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back, or the buttocks. On many occasions, a primary presenting complaint of CPP may involve several discreet locations, organ systems, and anatomic areas. It is often useful to ask the patient to list individual areas of pain during the visit or have the patient designate locations of pain on an anatomical map of the human body. Assessment of anatomic sites of pain may differentiate between a nonvisceral (distribution in a dermatomal pattern) source, which is well localized, or a visceral origin of pain, which is not well localized. For example, pain which is both dorsal and ventral often suggests intrapelvic pathology, whereas only dorsal lower back pain suggests a musculoskeletal etiology [2]. In the situation of visceral pain, it is often difficult for the patient to differentiate gynecologic, urological, or gastrointestinal symptoms [2].
- Pain severity and quality
  It is well recognized that perception of pain is subjective. As a result, rating pain in an objective fashion is often problematic. Utilizing adjectives such as "mild," "moderate," or "severe" to describe pain severity is not sensitive enough to detect subtle gradations of pain changes, nor does it provide an adequate means to follow the response of pain following treatment. More objective methods to quantify pain involve the use of pain scoring systems such as the McGill Present Pain Index and Visual Analog Scale [22]. With these methods, rating of pain may be

performed more consistently by patients and interpreted in a more standardized fashion by clinicians. As is the case for severity of pain, it can be challenging to assess the quality of pain. In order to gain an accurate assessment of both severity and quality, it is useful to inquire about the duration of pain after the initial onset of symptoms, how the severity and nature of the pain has changed during a designated time period, and how symptoms have negatively impacted the patient's ability to perform daily personal and professional activities.

- Timing of pain onset and resolution
  Establishing a temporal relationship for the onset or exacerbation of symptoms can be useful in some clinical scenarios. Exacerbation of chronic symptoms related to the onset of menses or those symptoms consistently occurring during a specific phase of the menstrual cycle (e.g., follicular or luteal phases) when anticipated monthly hormonal changes of the menstrual cycle occur may suggest a gynecologic etiology such as endometriosis, uterine fibroids, adenomyosis, or pelvic congestion syndrome. However, there is no consistent pattern of symptoms which will always confirm a gynecologic origin. In fact, those CPP symptoms which may seem to be gynecologic in origin may also simultaneously involve underlying gastrointestinal, urological, and musculoskeletal etiologies. A classic example includes the exacerbation of irritable bowel syndrome and inflammatory bowel syndromes resulting in the exacerbation of pelvic pain in the late luteal phase just prior to the onset of menses.
- History of underlying psychiatric disease
  The presence of depression or somatization disorders may certainly impact a patient's perception of the severity and quality of symptoms. In the case of depression, which can be one of the many predictors of pain severity in women with CPP, it can also prove to be a significant predictor of response to treatment. In the case of a somatization disorder, patients who persistently complain of a diversity of physical symptoms that have no identifiable physical origin will typically visit many doctors in pursuit of an effective treatment. To this end, it is necessary to access for underlying psychiatric disorders which may contribute to CPP or may impede improvement following medical intervention.
- Alleviating or exacerbating factors
  In some situations, identification of maneuvers or stimuli which reduce or increase symptoms may implicate and exclude specific etiologies. Given the close proximity of the gynecologic, urological, and gastrointestinal systems, and the significant overlap of symptoms and signs of these different systems, it may be difficult to consistently confirm a specific etiology of gynecologic or nongynecologic origin. Exacerbation of symptoms involving the lower back or abdomen following physical exertion may suggest a musculoskeletal origin. Additionally, dietary or medical modifications, which may alleviate persistent gastrointestinal symptoms (e.g., diarrhea, constipation, flatulence) and CPP simultaneously, may implicate a gastrointestinal origin and lower suspicion for a gynecologic etiology.

- Associated nongynecologic symptoms and signs
  Some aspects which may make a gynecologic origin less likely include isolated gastrointestinal symptoms unrelated to the menstrual cycle, points of discreet tender areas of the abdominal wall outside of the anatomic pelvis, and complaints of specific areas of pain just below or just above the umbilicus extending to the right upper quadrant. Unfortunately, gynecologic and urological causes may be difficult to differentiate given the close proximity of the bladder to the apex of the vaginal vault and the anterior aspect of the uterus.
- Prior and current opioid use
  In any medical condition which may require opioids for pain relief, the clinician's goal is to administer the minimum amount of medication to achieve a reasonable therapeutic effect. It is recommended that universal precautions be applied to the use of opioids in the management of pain because of the concerns about misuse, diversion, and addiction [23]. Although the risk for addiction is approximately 7.5% in the general population [24], it is estimated that it may be as high as 15–23% in the pain population [25]. The key elements of this approach to care include the following:

  1. A pain diagnosis must be established with a reasonable differential.
  2. Consider psychological assessment.
  3. Institute an opioid treatment agreement.
  4. Assess pain level and function at each visit.
  5. Avoid opioid monotherapy.
  6. Monitor compliance with periodic random urine drug screens.
  7. Adhere to strict documentation guidelines.
  8. For new patients to the practice, obtain all prior records prior to initiating opioid therapy.

Physical Examination

Following a thorough history, the clinician may formulate a differential diagnosis comprised of the most likely and least likely etiologies for CPP. In many instances, it may be unclear whether symptoms are caused by either gynecologic or nongynecologic etiologies or both. However, the information gathered from the history will provide the foundation of this critical portion of the office visit and enable the provider to perform a focused physical examination. The major goal of the examination is to detect the approximate anatomical location(s) of tenderness and correlate these findings with the patient's complaints. To ensure precision and accuracy, the clinician should employ a systematic approach with every examination regardless of the nature and severity of CPP. The ultimate goal of the examination is to

reproduce pain (similar in nature to original chief complaint) by palpation or positioning. Most importantly, the patient should be asked whether the pain produced during the examination is the pain for which they are being evaluated.

In addition to the gynecologic/reproductive system, the urological, gastrointestinal, musculoskeletal, neurological, and psychological systems should also be evaluated [2]. When focusing on gynecologic etiologies for CPP, the physical examination can be divided into the supine (abdominal exam) and dorsal lithotomy (positioned in stirrups with speculum exam, bimanual exam, rectovaginal examination, palpation and inspection of vaginal and perineal mucosa and musculature) portions. With regard to urological etiologies, the same positions as the gynecologic exam apply. Special attention to the urethral orifice, anterior vaginal wall just beneath the bladder and posterior aspect of the urethra (during bimanual examination), and the costovertebral angles should be applied during the abdominal examination. The gastrointestinal system will also utilize similar positions of the gynecologic and urological as well as supine examination. A much different approach may be utilized for the musculoskeletal system and will require standing, sitting, supine, and lithotomy positions.

Supine Position

The supine position provides the best means to mainly assess the gastrointestinal and musculoskeletal systems. Before starting, the clinician should ask the patient which areas are most painful. Initial maneuvers involve the standard approach of superficial and deep palpation in all four quadrants of the abdomen. The most painful areas, which have been acknowledged by the patient at the beginning, should be palpated last to avoid unnecessary distraction for the duration of the exam. It is also most helpful if the patient can maintain relaxation of the abdominal musculature. With initial superficial palpation, the clinician can assess for focal areas of discomfort of the abdominal wall, which may be significant for hypersensitivity of the skin (hyperalgesia) or myofascial trigger points [2]. A simple maneuver, the Carnett test, is useful to differentiate between abdominal wall (e.g., myofascial) and visceral tenderness [26]. In this test, the area of pain is palpated, and the patient voluntarily tenses the abdominal muscles by raising the head or legs. If pain increases with this motion, this suggests that it is of myofascial origin. If pain is decreased or unchanged, it is more likely that it is not of myofascial origin. Attention should also be directed to the usual components of the traditional abdominal exam: assessment of bowel sounds, masses, ascites, rebound tenderness, guarding, and palpation of pelvic masses in the abdomen (e.g., fibroid uterus, large adnexal mass(es), metastatic gynecologic or gastrointestinal malignancy).

An often overlooked aspect of the supine examination is the investigation of hernias in both the inguinal and abdominal regions. In the standing, sitting, and supine

positions, any masses in the inguinal area above and below the femoral region should be assessed with and without patient providing motions of valsalva. The clinician should also take special attention to any abdominal scar(s) from prior surgery. Prior incisions in areas such as the umbilicus (e.g., prior laparoscopy, postpartum tubal ligation), right lower quadrant (e.g., prior open appendectomy, laparoscopy), or just above the pubic symphysis (e.g., previous cesarean section, open hysterectomy, or prior laparotomy) require a similar examination as the classic inguinal hernia. Specifically, hernia(s) may be located at the site of prior incision(s) as well as the medial and lateral aspects of the rectus muscle bundle (i.e., spigelian hernia). When palpating the lower abdomen, care should also be taken to palpate the bladder (e.g., interstitial cystitis) and the pubic symphysis for tenderness (e.g., osteitis pubis, osteomyelitis, undetected separation of the symphysis during prior childbirth).

Musculoskeletal etiologies can also be elicited during the supine exam. Lower back dysfunction may be recognized by weakness and stiffness in the lumbar spine. The traditional obturator and psoas signs may also be recognized during leg flexion and knee to chest maneuvers [27].

Dorsal Lithotomy Position

External Pelvic Examination

Given the anticipated anxiety, which may be present when performing the pelvic and bimanual examination in the lithotomy position, this portion will require the clinician to be especially sensitive and receptive to the patient's feedback and potential sense of vulnerability. This initial segment will involve visual inspection of the external genital and perineum for lacerations, excoriations, erythema, fistula, fissures, masses, abscesses, atrophy, or evidence of trauma or abuse. In addition to inspection, a basic sensory examination can be performed with single digit or cotton swab to assess pain in the vestibule, posterior forchette, labia, as well as musculature of the pelvic floor.

Speculum Examination

This portion of the gynecologic exam involves placement of the speculum for the purpose of visual inspection of the introitus, vaginal mucosa, posterior and anterior fornices, and the uterine cervix for abnormalities and tenderness. In patients who have undergone hysterectomy, it is crucial to assess for tenderness of the vaginal cuff and ensure that there are no defects or herniated pelvic contents (e.g., residual fallopian tubes, ovaries, and bowel) in the mucosal edges at the apex. Appropriate cytologic and bacteriologic specimens may also be obtained.

Bimanual Examination

This is perhaps the most crucial segment of the physical examination in women since the gynecologic, urological, gastrointestinal, and musculoskeletal systems may be assessed simultaneously. This exam begins with the clinician providing ample notice of pressure with insertion of a single index finger. With this initial maneuver, the provider may first assess for discreet pain in the musculature (levator ani, piriformis, coccygeus, and obturator internus) of the pelvic floor. In patients with pelvic floor dysfunction/pain, their original symptoms may be reproduced. Previously described disorders such as vulvar vestibulitis, pelvic floor myalgia, piriformis syndrome, levator ani spasm syndrome, and coccydynia, which appear similar to pelvic floor pain, may be discovered during the initial maneuvers of the bimanual exam [2, 28–30]. If the patient is comfortable with a single index finger, the clinician may attempt to use both index and middle finger during the digital exam.

The anterior vaginal, urethral, and trigonal areas should be palpated to assess for any masses, tenderness, induration, or abnormalities suspicious for urological etiologies such as chronic urethritis, urethral diverticulum, vaginal wall cyst, or interstitial cystitis. At the next level of the exam, attention should be turned to the posterior and anterior fornices, cervix, and uterus to assess for discharge, masses, irregularities, and nodularities. Cervical motion tenderness, limited mobility of the uterus, and uterine fundal tenderness may raise suspicion for gynecologic processes such as chronic pelvic infection (pelvic inflammatory disease), endometriosis, uterine fibroids, and adenomyosis. At the completion of the bimanual exam, a rectovaginal examination should be performed to assess for rectal masses, nodularity and rigidity of the uterosacral ligaments (ligaments connecting the cervix and uterus to the vaginal cuff), as well as uterine position (retroverted, anteverted, axial). Tender or nodular uterosacral ligaments in tandem with a fixed, immobile uterus with retroverted position may raise suspicion for processes such as endometriosis or pelvic adhesive disease.

Diagnostic Studies

With technologic advances of the past two decades, there is a plethora of testing available in the contemporary era of medicine. Many older diagnostic tests have become outdated and obsolete, while newer tests have replaced their predecessors as gold standards. As was the case several decades ago, when there were many fewer diagnostic tests available, a comprehensive history and physical examination is still the foundation of the differential diagnosis prior to the implementation of any diagnostic study. To this end, diagnostic tests may serve to confirm the provider's clinical suspicion based upon the history and examination. Ordering of clinical tests should be performed in a focused manner and is dictated by the provider's suspicion for the most likely condition(s) to account for symptoms (Tables 4.1 and 4.2).

Table 4.2 Summary of symptoms and potentially useful diagnostic testing for common conditions associated with chronic pelvic pain

Condition	Symptoms	Testing
Endometriosis	Dysmenorrhea, dyspareunia, abdominopelvic pain, dyschezia, dysuria, lumbosacral pain	Urine C&S GC/CT cervical culture Pelvic ultrasound
Uterine leiomyomata (fibroids)	Dysmenorrhea, menorrhagia, metrorrhagia, anemia, pelvic pressure, bloating, abdominopelvic pain, early satiety, constipation, urine frequency or hesitancy	Pelvic MRI (as indicated) Sonohysterogram CBC Pelvic ultrasound
Adenomyosis	Dysmenorrhea, menorrhagia, metrorrhagia, bloating, abdominopelvic pain, pelvic cramping radiating to back, rectum, and thighs	Pelvic ultrasound Pelvic MRI (as indicated)
Pelvic adhesive disease	Abdominopelvic pain, dyspareunia, dysmenorrhea, dyschezia, constipation, bowel obstruction	Pelvic ultrasound Abd/pelvic CT (as indicated) Colonoscopy
Pelvic congestion syndrome	Deep dyspareunia, postcoital pain, dysmenorrhea extending after menses, shifting location of pain	Pelvic ultrasound (+/− Doppler) Pelvic venography
Inflammatory disease	Focal pelvic pain, vaginal discharge, metrorrhagia, fever, nausea	GC/CT cervical culture Wet mount Pelvic ultrasound Pelvic MRI (suspected tubo-ovarian abscess)
Interstitial cystitis	Dysuria, urinary urgency, urinary frequency, abdominopelvic pain, dyspareunia	Urine C&S Cystourethroscopy
Irritable bowel syndrome	Abdominopelvic pain diarrhea, constipation	GI referral colonoscopy (as indicated)

C&S culture and sensitivity, *GCCT* gonorrhea and chlamydia, *CBC* complete blood count, *MRI* magnetic resonance imaging, *CT* computed tomography, *GI* gastroenterology

Imaging

Transvaginal ultrasound is quite useful for real-time assessment of the pelvis. This modality is most effective for the detection of pelvic masses (adnexal, some gastrointestinal tumors, uterine fibroids) as well as characterization of the uterus and adnexa. More resource intensive options such as magnetic resonance imaging (MRI) or computer tomography (CT) may be considered if the findings of the ultrasound are abnormal or equivocal.

Laboratory Testing

It is desirable that test(s) will be ordered when the results will change the diagnosis, and/or impact future evaluation and treatment. Please refer to Table 4.2 for a list of pertinent diagnostic tests for common causes of CPP. A comprehensive discussion of these tests is beyond the scope of this chapter.

Procedures

Diagnostic Laparoscopy

As mentioned previously, 40% of all laparoscopies performed annually are for the indication of CPP [10]. Notably, endometriosis and pelvic adhesive disease comprise approximately 85% of all laparoscopic diagnoses in women with CPP [10]. It is necessary to counsel patients that 30–50% may have a negative laparoscopy (normal intraoperative findings) despite an elevated preoperative suspicion for pathology. To this end, it is important to be very selective with the use of laparoscopy and to base the decision for surgery upon findings of patient history, physical exam, laboratory testing, and imaging. When specific diagnoses such as endometriosis and/or pelvic adhesive disease are suspected based upon intraoperative visual inspection, surgical sampling and histopathologic examination are recommended since this method has proven more reliable than visual inspection alone. Relief of symptoms may be achieved by excision and ablation of endometriosis and adhesions during laparoscopy.

Endoscopy

By virtue of the significant frequency of gastrointestinal symptoms in patients with CPP, many are referred to gastroenterology for the evaluation of possible gastrointestinal etiologies. Given the significant overlap of gastrointestinal and gynecologic symptoms, the clinician should have a low threshold for referral to gastroenterology. Although a large proportion of patients with CPP will be diagnosed with irritable bowel syndrome, many patients will still undergo colonoscopy to exclude other forms of gastrointestinal pathology.

Etiologies

It is beyond the scope of this chapter to cover all causes in each category in extensive detail. The most common gynecologic etiologies encountered in women with CPP will be discussed herein.

Gynecologic

Endometriosis

Background

Endometriosis is a common gynecologic disorder affecting reproductive-aged women [31–38]. It is characterized by the presence and proliferation of endometrial tissue (tissue lining the uterus) outside of the uterus [34]. The disease is most commonly located in the female reproductive tract and usually involves the uterus, fallopian tubes, ovaries, as well as the peritoneal surfaces of the pelvis and abdomen. It affects approximately 10–15% of women of reproductive age and approximately 25–40% of women experiencing infertility [34]. It is estimated that > 10% of women undergoing surgery for a gynecologic indication will have endometriosis. Interestingly, this disorder will be discovered in 33% of women undergoing laparoscopy for CPP [39]. Possible risk factors associated with this disease include early menarche, menstrual interval less than 27 days, mullerian anomalies with vaginal and/or uterine obstruction of menstrual blood flow, and family history (first-degree female relative) [40, 41].

Etiology

The most commonly accepted etiology is retrograde menstruation (Sampson's theory). Other proposed pathways of pathogenesis include vascular or lymphatic transport of endometrial fragments and the transformation of coelomic epithelium into endometrial glands from an unspecified signal [42]. Altered systemic and local immune responses are also believed to contribute to the pathogenesis and clinical presentation of the disease [31, 33, 38, 43–45]. The glands and stroma of the ectopic endometrial tissue are responsive to sex steroid hormones (estrogen and progesterone) and undergo changes similar to those of the native endometrium during the menstrual cycle. As a result of these hormone-induced changes, endometriotic tissue can undergo hormone-induced proliferation, differentiation, and recruitment of a blood supply, resulting in pelvic adhesions, scarring, and distortion of the female reproductive tract.

Clinical Presentation

The signature symptoms of endometriosis are chronic pelvic pain, dyspareunia, and dysmenorrhea. The clinical manifestations of this disease are variable and unpredictable in both clinical presentation and response to treatment [46]. Interestingly, the symptoms associated with endometriosis may not correlate with the stage or extent of disease. This paradox may be explained by the contention that symptoms may be

caused more by local inflammation in the peritoneal cavity than by the extent of endometriosis implants. Ironically, many women with endometriosis may be asymptomatic. Overall, it is more likely to be diagnosed in women with the following symptoms: “abdominal and pelvic pain (odds ratio [OR=5.2], dysmenorrhea [OR=8.1], menorrhagia [OR=4.0], and dyspareunia [OR=6.0] compared to controls” [47].

The pelvic pain usually associated with endometriosis is classically described as secondary dysmenorrhea (pelvic pain beginning prior to the onset of menses and ending during or immediately following menses), dyspareunia with deep penetration during intercourse (exacerbated during menses), or back pain extending from sacrum to the coccyx. Because endometriosis implants may involve adjacent anatomical pelvic sites such as the bladder, bowel, anterior peritoneal wall, and sacral promontory, physiologic dysfunction of these organ sites may pose a confusing diagnostic picture comprised of simultaneous gynecologic and nongynecologic complaints. Specifically, perimenstrual tenesmus, diarrhea or constipation, and dyschezia may be observed in cases of bowel involvement, and dysuria and hematuria may be experienced in cases of bladder involvement. Ironically, bladder or bowel symptoms may be present without direct involvement of endometriosis of these organ systems [48, 49]. Painful defecation during menses and severe dyspareunia may be the most predictable symptoms of deeply invasive endometriosis [50]. Frequently, existing constant baseline pain symptoms may be exacerbated during menses.

Diagnosis

Findings of the physical examination can be variable and may be dependent upon the site of disease. In some cases, there are no abnormalities discovered. The most common findings are tenderness in the posterior vaginal fornix and/or adnexa during bimanual examination. Additional findings may also include:

- Fixed, immobile uterus in retroverted position
- Lateral displacement of cervix (observed during speculum examination)
- Tenderness elicited with movement of cervix and/or uterus
- Thickened, indurated, or nodular uterosacral ligaments during rectovaginal examination
- Enlarged, tender, or fixed adnexa
- Palpable nodularity in rectovaginal septum or posterior cul-de-sac during rectovaginal examination

The diagnosis of endometriosis can only be made by direct visual inspection of disease during laparoscopy or laparotomy with the confirmation of endometrial glands and stroma during microscopic examination of surgical specimens (Fig. 4.1). There are no definitive serum markers or imaging modalities that can consistently confirm or exclude the presence of disease. Imaging studies may only be useful in the case of an ovarian endometrioma (endometriosis cyst of the ovary). The typical “ground glass” appearance of an endometrioma will be characterized as a complex cyst with low-level echoes consistent with old blood (Fig. 4.2). Endometriosis lesions of the peritoneum, bladder, or bowel are not typically detected by pelvic

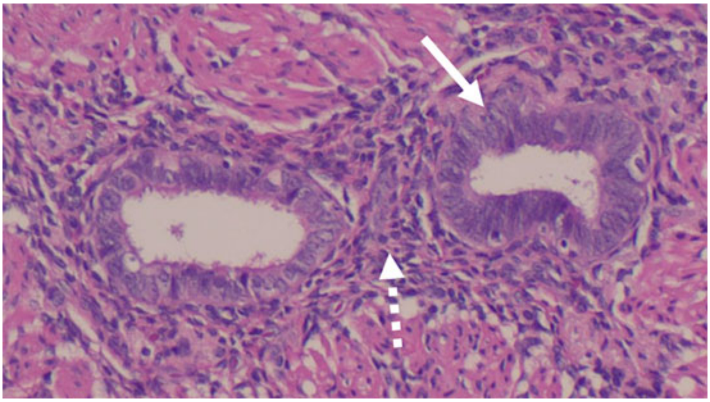

Fig. 4.1 *Microscopy, endometriosis*. Microscopic image demonstrating endometrial glandular (*solid arrow*) and stromal (*dashed arrow*) components typical of endometriosis (Used with permission of Drucilla J. Roberts MD. Department of Pathology, Massachusetts General Hospital, Boston, MA)

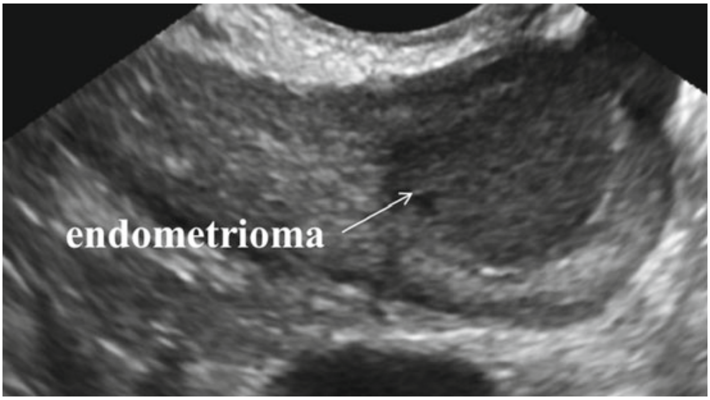

Fig. 4.2 *Pelvic ultrasound, endometrioma.* Pelvic ultrasound demonstrating ovarian endometriosis (*endometrioma*) (Used with permission of Susanna I. Lee MD PhD, Department of Radiology, Massachusetts General Hospital, Boston, MA)

ultrasound, MRI, or CT. One exception is deeply infiltrating endometriosis of the rectum or rectovaginal septum, which may be detected by a combination approach of transvaginal and transrectal ultrasound [51–53]. Serum biomarkers (e.g., CA125) have not proven sensitive or specific enough for long-term surveillance following the initiation of medical or surgical therapy.

Treatment

In the majority of cases of CPP in women of reproductive age, endometriosis is the presumptive diagnosis based upon a predominance of gynecologic symptoms.

After other etiologies have been excluded, an appropriate initial approach will involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for relief of pain. If this initial intervention does not produce desired relief, additional options include the use of combination oral contraceptive pills (OCPs), long-acting progestins (depot intramuscular or oral medroxyprogesterone acetate), GnRH agonist, danazol (17 alpha-ethinyl testosterone derivative), aromatase inhibitors, and levonorgestrel intrauterine device (IUD). In the case of systemic hormonal therapy, a hypoestrogenic state is induced to reduce proliferation of the glandular and stromal components of endometriosis implants. Those options utilizing progestins aim to induce atrophy of the endometriosis lesions. Prior to the initiation of any therapy, the clinician should review the side effect profiles of all agents.

In many cases, first-line therapy will include a trial of OCP with NSAIDs. If significant dysmenorrhea or exacerbation of CPP during menses continues, a continuous course of OCP may be initiated where only active hormonal pills are utilized for 3–4 months at a time to reduce the number of menses. This approach with continuous OCPs was found to provide significant reduction in baseline pain compared to cyclic OCP use [54]. Of note, there is no individual combination OCP formulation, which has been shown to have superior efficacy. If continuous OCPs and NSAIDs are not effective, a 3–6-month trial of GnRH agonist or an intramuscular depot progestin has been supported by the literature [55]. If these interventions are not effective, the clinician may consider additional second- and third-line medical options such as progestins, danazol, aromatase inhibitor, or levonorgestrel intrauterine device (IUD). If these options are not utilized, then diagnostic laparoscopy may be offered and performed to confirm the diagnosis, exclude other causes for symptoms, and possibly provide relief of symptoms via excision/ablation of disease if found to be present.

If multiple medical options are not effective following confirmation of endometriosis during laparoscopy, and laparoscopic excision of disease is unsuccessful as well, more complex surgical procedures such as hysterectomy with removal of both ovaries or presacral neurectomy may also be considered. The indication for these procedures in the setting CPP will be covered later in this chapter. If disease symptoms are especially significant and refractory to several different treatment options, referral to a gynecologist or reproductive endocrinologist with expertise in endometriosis is recommended.

Uterine Leiomyomata (Fibroids)

Background

Human leiomyomata (fibroids) are benign smooth muscle tumors of the uterus and represent the most common neoplasms in women of reproductive age. The lifetime incidence of fibroids is approximately 60% in the general population [56]. However, women of African-American descent are disproportionately affected, with an estimated incidence of 80% in several epidemiological studies [56]. Despite the high

incidence of uterine fibroids in the general population, only 20% of women with fibroids report significant symptoms and seek medical consultation for this gynecologic condition [57, 58].

Etiology

Despite the first formal description of uterine fibroids in the sixteenth century, the pathogenesis of this disorder remains unclear. Specifically, the underlying mechanisms of development, recurrence, location, progression of growth, and the variable incidence in different ethnic groups have not been elucidated clearly. These benign tumors are estrogen and progesterone responsive with a polygenic inheritance pattern [58]. The most commonly accepted etiology is the transformation of myometrial smooth muscle (comprises majority of uterine muscle mass) fibroblasts. Ovarian steroid hormone action in fibroids is mediated by a complex array of endocrine, autocrine, paracrine, and genetic events. As a result, the specific functional role of growth factors, chemokines, and cytokines in cellular transformation, proliferation, apoptosis, neovascularization, and cellular hypertrophy has been difficult to characterize with certainty [59]. The cytokine, transforming growth factor beta (TGF-β) and its cognate receptor (TGF-βR), and microRNAs (miRNAs) have been recently implicated by many investigators as crucial players in the genesis of uterine fibroids [60, 61].

Clinical Presentation

The most common clinical symptoms include heavy and prolonged menstrual bleeding, anemia (secondary to excessive menstrual blood loss), pelvic pain and pressure, dysmenorrhea (painful menses), urinary incontinence, constipation, lower back pain, sexual dysfunction, infertility, recurrent pregnancy loss, and compression of adjacent pelvic organs by especially large uterine fibroids. In some symptomatic patients, surgical removal of fibroids with preservation of the remaining uterus (myomectomy) may provide relief of symptoms. However, a significant degree of morbidity is associated with uterine fibroids, and removal of the uterus (hysterectomy) may be the only option for definitive cure. Symptomatic uterine fibroids remain the leading indication for hysterectomy in the United States (USA), with approximately 200,000 hysterectomies performed annually [62]. Most notably, financial analyses estimate an annual cost to the US health-care system of $2 billion dollars for this benign gynecologic disorder [63].

Diagnosis

Depending upon the size, number, and location of fibroid(s), the uterus may be of normal size or significantly enlarged. Fibroids may be classified according to

location: submucosal (endometrial cavity), intramural (within the myometrium), or subserosal (external to myometrium but within the boundaries of the uterine serosa). The initial steps for diagnosis include an abdominal and pelvic examination (bimanual examination) to assess the size and mobility of the uterus, but also to assess any palpable fibroids (mobile or fixed masses in the expected anatomic location of the uterus). Depending upon the clinical presentation, the uterus may be tender during deep bimanual palpation in some patients. The typical size of a normal uterus will be approximately 6–8 cm in length and will have the approximate size of an apple. In the case of significantly large or numerous fibroids, the enlarged uterus may extend to the xyphoid process and approximate the size of a 40-week gravid uterus. Additionally, a complete blood count (CBC) should be obtained to exclude anemia in the setting of heavy or prolonged menses.

If leiomyomata are suspected, a pelvic ultrasound should be obtained to assess uterine size as well as location and size of the fibroids (Fig. 4.3a). In the case of extensive fibroid involvement of the uterus or planning for surgical therapy, a saline sonohysterogram or pelvic MRI (Fig. 4.3b) may be obtained to further characterize fibroid location. If a uterine fibroid is thought to be submucosal on a pelvic ultrasound, an office hysteroscopy or saline sonohysterogram may be performed for confirmation.

Treatment

The treatment of choice for uterine fibroids may be dependent upon several factors including the nature and severity of symptoms as well as desire for future childbearing. If presenting symptoms are primarily comprised of excessive and/or irregular bleeding, a medical approach may be considered initially. In this clinical scenario, hormonal therapy options, such as OCPs, progestins, levonorgestrel IUD, and GnRH agonists, may be utilized to minimize or eliminate menses.

In the setting of chronic abdominal pelvic pain and pelvic pressure, symptoms are frequently attributed to fibroid necrosis and/or significant enlargement of the fibroid uterus with compression of adjacent organs ("bulk symptoms"). In this situation, the goal of therapy is to induce uterine quiescence and reduce fibroid volume and uterine size. This may be achieved medically with the use of a GnRH agonist. However, due to significant side effects related to hypoestrogenism and the risk of osteopenia with long-term use, this may only be used on a temporary basis to induce amenorrhea to correct anemia or reduce uterine size in preparation for surgical therapy.

If medical therapy is not selected or indicated, surgical therapy may be considered as reasonable approach. If a patient desires pregnancy in the future, surgical removal of the fibroids with preservation of the uterus (myomectomy) may be performed by either hysteroscopy (submucosal fibroid), laparoscopy (intramural, subserosal), or laparotomy (intramural, subserosal). Myomectomy provides effective relief of symptoms for many patients. However, uterine leiomyomata may have a recurrence

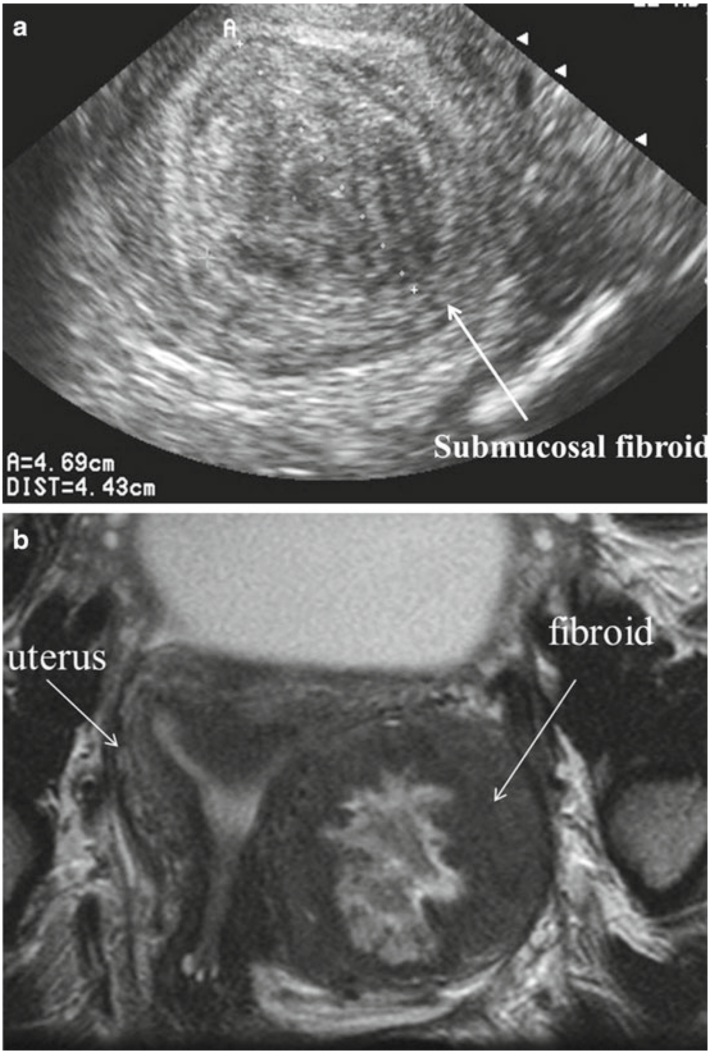

Fig. 4.3 *Radiographic imaging, uterine fibroid.* Pelvic ultrasound (**a**) and MRI (**b**) images of uterine fibroid (*arrows*) (Used with permission of Susanna I. Lee MD PhD, Department of Radiology, Massachusetts General Hospital, Boston, MA)

rate of 20–80% over a 5–10-year period [56, 62]. If the recurrence risk of fibroids is unacceptable to a patient, she is not interested in future pregnancy, and she prefers definitive therapy, then hysterectomy (via laparoscopy or laparotomy) is an appropriate option. In patients who wish to avoid surgical therapy and do not desire future childbearing, the alternative option of uterine artery embolization may also be considered and has demonstrated good results in specific subsets of patients [64].

Adenomyosis

Background

Adenomyosis is characterized by the presence of endometrial tissue (inner lining of the uterus) in the myometrium (muscular layer) of the uterus. In this medical condition, ectopic endometrium is the hallmark diagnostic sign. Previously named *endometriosis internus*, there is no evidence that this disorder has a common pathogenesis to endometriosis, although these two diseases are only found together in 10% of cases [65]. Risk factors associated with this condition include prior history of cesarean delivery, uterine surgery, pregnancy, tubal ligation, and pregnancy termination [65]. It is typically diagnosed in the fourth and fifth decades of life. However, the exact prevalence of the disorder is unknown.

Etiology

The exact cause of this disorder remains uncertain. It is speculated that adenomyosis results from the invasion of the myometrial layer by portions of the endometrial layer of the uterus. To this end, surgical disruption of the boundaries of endometrium and myometrium has been proposed as a possible mechanism for disease [66, 67]. Evidence in several animal models also suggests that elevated gonadotropins (e.g., follicle-stimulating hormone) and lactotrophs (e.g., prolactin) may also contribute to the induction of disease [68, 69]. Additional evidence of aberrant interleukin-18 (IL-18) and leukemia inhibitory factor (LIF) function has been of recent interest as a potential cause of disease [70, 71].

Clinical Presentation

The classic symptoms of adenomyosis include menorrhagia or metrorrhagia with associated dysmenorrhea. Unfortunately, many clinicians will attribute these symptoms to the perimenopausal transition since the most common period of diagnosis for adenomyosis is in the fourth and fifth decade. As a result, this diagnosis may be overlooked in women of this age group with these specific symptoms. This disorder may also pose a diagnostic dilemma as there is no characteristic clinical presentation. Nonclassic symptoms may also include CPP exacerbated at midcycle and the time of menstruation. Interestingly, many women will also endorse simultaneous symptoms of intense pelvic cramping and vaginal pressure radiating to the lower back, groin, rectum, and anterior thighs. Others who have experienced childbirth will describe the pelvic cramps as "contractions of labor" and will have a sensation to "bear down" in a similar fashion to pushing during the second stage of labor.

The physical examination is extremely variable. Findings that may raise suspicion include a slightly to moderately enlarged uterus with a globular contour and

mild fundal tenderness during bimanual examination. Findings of vaginal forniceal tenderness and abdominal pain are less common. Notably, fundal tenderness may be more pronounced when the bimanual examination is performed during the late luteal phase or menses compared to the remainder of the menstrual cycle. Despite the sensation of vaginal and lower back pressure, there is usually no evidence of pelvic organ prolapse.

Diagnosis

Pelvic ultrasound is a cost-effective initial diagnostic test. Typical findings on ultrasound include heterogeneous echotexture of the myometrium containing several echogenic foci (presumed to be discrete islets of endometrium). Unfortunately, this test may only raise suspicion for this disorder and is not confirmatory of the diagnosis. Confirmation of this disorder is only possible with microscopic examination of the surgical hysterectomy sample. Characteristic microscopic findings include identifiable areas of endometrial glandular and stromal epithelium within myometrial muscular fibers.

MRI or 3D ultrasound provides superior diagnostic potential for adenomyosis compared to pelvic ultrasound. However, as in the case of ultrasound, it does not confirm the diagnosis. With the improved spatial and contrast resolution, MRI provides reasonable imaging of the myometrium with demonstration of interspersed hyperintense foci (dilated endometrial glands and acute hemorrhage with iron deposition) on T2 imaging (Fig. 4.4). An additional MRI characteristic suspicious for adenomyosis include thickened junctional zone at the myometrial/endometrial interface of >12 mm [72].

Treatment

In many cases, the primary complaint during initial presentation is heavy and prolonged menstrual bleeding with exacerbation of pelvic pain during menses and midcycle. The goal in this situation is to facilitate uterine quiescence by suppression of ovarian production of stimulatory sex steroids (e.g., estradiol). As was the case in the treatment of uterine leiomyomata, hormonal therapy with OCPs, progestins, or GnRH agonists serve as first-line options for both bleeding and pain symptoms. The levonorgestrel IUD has been shown to provide promising results for the control of excessive menstrual bleeding, but not pain, bloating, or cramping symptoms [73].

If medical therapy proves unsuccessful, there is a limited armamentarium of available surgical options. In the case of menorrhagia and metrorrhagia, a hysteroscopic endometrial ablation may be performed to achieve reduced menstrual flow or secondary amenorrhea. Unfortunately, there are no reliable data available to predict failure rates following this option. If childbearing has been completed, and all other options are unsuccessful, then hysterectomy is the definitive surgical option.

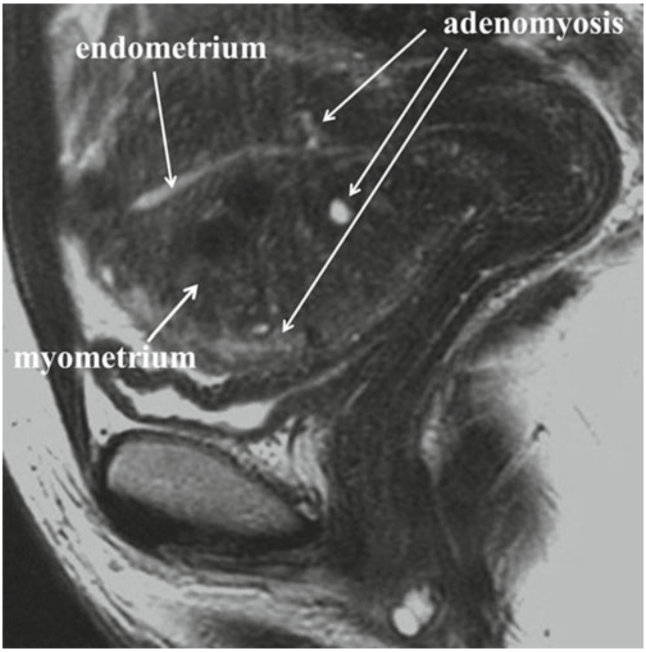

Fig. 4.4 *Magnetic resonance imaging, adenomyosis*. Pelvic MRI images of adenomyosis demonstrating enlarged globular appearance of uterus with increased intensity foci (*arrows*) in the myometrium (Used with permission of Susanna I. Lee MD PhD, Department of Radiology, Massachusetts General Hospital, Boston, MA)

Adhesive Disease

Background

Adhesions are defined as connections between opposing serosal and nonserosal surfaces of intra-abdominal organs, the abdominal wall, and other areas which should not be connected otherwise [74]. The connection may be a vascular or avascular band with variable opacity (transparent, semiopaque, or opaque) and thickness (filmy or dense) or may involve the intimate connection of surfaces without an identifiable band. The exact role of abdominopelvic adhesions in CPP remains controversial. Although the underlying contribution of adhesive disease in infertility and gastrointestinal obstruction is self-evident, the relationship between CPP and adhesions is incompletely understood [74]. Adhesions are a natural consequence of surgical tissue trauma and healing and may also occur following infection or tissue damage.

Based upon the large postoperative database of the Surgical and Clinical Adhesions Research (SCAR) Group, approximately a third of patients who underwent an open abdominal or pelvic surgery were readmitted an average of two times within 10 years of their original procedure due to complications of postoperative adhesions [75]. Among those undergoing gynecologic procedures, there was

a comparable risk of adhesion-related hospital readmission for both open and laparoscopic procedures. Ovarian surgery and hysterectomy yielded the greatest risk for readmission in this group [76, 77].

Etiology

Adhesions are caused by tissue trauma during sharp, mechanical or thermal injury, infection, desiccation, abrasion, or foreign body reaction which triggers a cascade of events beginning with the disruption of stromal mast cells, release of vasoactive substances (e.g., histamine and kinins) and resulting in vascular permeability [78]. As a result of vascular permeability, fibrin deposits containing leukocytes and macrophages accumulate and healing occurs following fibrosis and mesothelial regeneration [79, 80]. The vast majority of fibrinous exudates break down within 72 h, but trauma-induced local suppression of peritoneal fibrinolysis predisposes their organization into adhesions [78, 79].

It is hypothesized that the symptoms associated with CPP may be caused by distortion of pelvic anatomy, impairment of visceral organ mobility, or stretching of the adhesion and the attached organ or peritoneum [78–80]. Although the presence of nerve fibers has been confirmed in adhesions, there is no difference in the quantity of these fibers in the adhesions of patients with or without CPP [81]. As was the case for endometriosis, there is no consistent relationship between the extent of adhesions and severity of pain. Previous studies demonstrating painful adhesions during conscious laparoscopic pain mapping have not provided convincing evidence for a direct causality to symptoms [82]. Although some investigators have reported improvement of pain following lysis of adhesions, one randomized clinical trial demonstrated that only women with dense bowel adhesions reported a reduction in pain following adhesiolysis [83].

Clinical Presentation

Risk factors for pelvic adhesions include a history of prior surgery, pelvic inflammatory disease (PID), perforated visceral organ (resultant bacterial and chemical peritonitis), endometriosis, inflammatory bowel disease, radiation therapy, and long-term peritoneal dialysis [84]. Unfortunately, when seeing a patient with CPP, it is not only difficult to confirm the presence of adhesions from the history, but it is often unclear if pelvic adhesive disease may be the primary or secondary etiology of symptoms.

Given the extremely variable presentation of this disorder as well as the unknown relationship to symptoms, this disorder poses one of the greatest diagnostic challenges. It would seem reasonable to assume that pelvic adhesive disease involving the female reproductive tract would primarily account for CPP. However, the cause of pelvic pain in this disorder may be made more confusing by the fact that adhesions of the large and small bowel may play a role in pelvic pain and many women will have the occurrence and reoccurrence of pelvic pain after removal of the uterus, fallopian tubes, and ovaries [74, 85]. The spectrum of symptoms range

from mild intermittent abdominopelvic pain to constant pain with gastrointestinal (constipation, bloating, dyschezia), gynecologic (dyspareunia, dysmenorrhea, focal lateral or central pelvic and adnexal pain), and musculoskeletal symptoms (abdominal wall tenderness).

Diagnosis

Ironically, many of the clinical findings of symptomatic pelvic adhesive disease may mimic those of endometriosis. This raises a particularly challenging conundrum when endometriosis and pelvic adhesive disease are present together [74]. Firstly, it is unclear if the adhesive disease is a result of endometriosis, and secondly, it may be uncertain if endometriosis and/or adhesions are the cause of CPP. Physical examination findings which may raise suspicion for adhesive disease include:

- Fixed, retroverted uterus with limited mobility
- Cervical motion tenderness or uterine fundal tenderness
- Posterior vaginal forniceal and/or adnexa tenderness
- Fixed masses of anterior abdominal wall or posterior cul-de-sac (during rectovaginal exam)
- Prior surgical scars on the abdomen

Although the initial diagnostic approach will be similar to endometriosis, there are no sensitive or specific laboratory or imaging tests. In some situations, the presence of pelvic or abdominal adhesive disease may be inferred from an abdominopelvic MRI or CT, which may demonstrate exaggerated displacement of visceral organs. If there are discrete gastrointestinal or urological symptoms, then additional procedures such as colonoscopy and/or cystoscopy may be considered to exclude significant visceral compromise by adhesions.

Treatment

In the scenario of a prior history of significant surgery, risk factors, or physical findings suspicious for adhesive disease, there is no gold standard proven treatment for consistent relief. As with the other potential causes of CPP, the clinician and patient should discuss the respective risks and benefits of a medical versus surgical treatment. If continuous symptoms are consistently exacerbated during specific portions of the menstrual cycle (e.g., menses, luteal phase, follicular phase), then a medical approach encompassing hormonal suppression of the cycle is a reasonable option. If there is no temporal exacerbation of baseline constant symptoms, all of the above medical options may be considered, as well as adjuvant NSAIDs and other forms of analgesics during acute exacerbations of pain. In some cases of significant symptomatic adhesive disease, the use of central and peripheral neuropathic medications (e.g., GABA analogues, tricyclic antidepressants) may be utilized following consultation with a pain specialist or physician experienced with the use of these drug classes.

In the case of failed medical therapy, surgical lysis of adhesions remains an option. Unfortunately, the risk of visceral injury increases with each subsequent procedure. Additionally, pelvic pain may be worsened by reformation of adhesions after multiple procedures. As mentioned previously, hysterectomy may be an option but does not consistently provide relief of symptoms in all patients [85].

Pelvic Congestion Syndrome

Background

Pelvic congestion syndrome (PCS) is defined as CPP associated with ovarian vein varicosities. Ovarian vein dilation is estimated to be present in 10% of women of reproductive age, with approximately 60% of these women at risk for development of PCS [86]. Unfortunately, this is still an underdiagnosed disorder given the nonspecific clinical symptoms and limited knowledge of this disorder by many health-care providers [87]. Given the limited study of this entity, and a paucity of standardized diagnostic criteria, this condition remains a controversial cause of CPP.

Etiology

The underlying mechanism of pelvic varicosities is reflux of blood in the ovarian veins. The primary hypothesized abnormality in this disorder is the malfunction or absence of functional valves within the ovarian veins, resulting in retrograde blood flow and eventual venous dilatation [88]. Unfortunately, the precise etiology of this disorder has not been determined.

Clinical Presentation

Pelvic varicosities have been associated with several mechanical compressive conditions such as uterine malposition, which may cause kinking of the ovarian vein, and the nutcracker syndrome where the left renal vein is compressed between the aorta and the superior mesenteric artery [88–90]. Additionally, this disorder is more common in multiparous women and has only been observed in reproductive-aged women. To this end, there is much speculation that ovarian sex steroids may play a significant role in the development of this disorder [91].

The cardinal presenting symptom is chronic pelvic pain, which is usually characterized as a dull ache which may be greater in intensity on one side of the pelvis. However, many patients will endorse shifting location of pain to the contralateral side intermittently. Characteristic symptoms may include deep dyspareunia, persistent postcoital pain, and an exacerbation of symptoms during the late luteal phase and with prolonged standing [88].

Diagnosis

During physical examination, observed signs may include vulvar varicosities that extend on to the medial thigh and distribution of long saphenous vein [88]. During bimanual examination, focal adnexa tenderness may be appreciated at the site of the ovary with deep palpation. Unfortunately, there are no characteristic physical signs described for this disorder.

Since incompetent and dilated pelvic veins are a common finding in asymptomatic women, there is much controversy as to whether this disorder is a pathologic entity [92]. To this end, there is heated debate as to the threshold limits for the measurement of pelvic vein dilation and flow. As a result, PCS may often be applied to cases with CPP and evidence of pelvic varicosities once the more common causes of CPP have been excluded with certainty.

If PCS is suspected, the clinician should initially confirm that the radiology staff of their institution is familiar and comfortable with performing imaging to estimate pelvic vessel diameter and Doppler flow. Transvaginal ultrasound diagnostic criteria for PCS include tortuous pelvic veins with diameter > 6 mm, slow blood flow or reversed caudal flow, dilated arcuate veins in the myometrium, communicating between pelvic varicose veins, and polycystic changes in the ovaries [87]. Pelvic MRI and multidetector CT (MDT) may also be utilized as indicated and within the scope of an institutional protocol.

Treatment

Historically, medical management with medroxyprogesterone acetate (MPA) was utilized to increase venous contraction [93]. However, there is no randomized data to demonstrate superior effects of MPA compared to other medical therapy options such as OCP and GnRH agonists. As a result, many clinicians may utilize the most familiar option during initial medical treatment attempts. In the event of failed medical therapy, many investigators have described the effective and successful use of transcatheter embolotherapy (TCE) to achieve ovarian vein occlusion. Prior to consideration of this therapy, consultation with an interventional radiologist and gynecologist with suitable experience with this treatment modality is recommended [94, 95].

Chronic Pelvic Inflammatory Disease

Background

Pelvic inflammatory disease (PID) is a term used to describe an infection of the upper female reproductive tract (uterus, fallopian tubes, and ovaries). It comprises a spectrum of inflammatory disorders including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis [96]. In the USA, greater

than 750,000 women are affected by PID each year, with the highest prevalence observed in teenagers and primiparous women [97]. CPP following acute PID may be more common than anticipated since approximately 66% of patients with laparoscopic evidence of previous PID were not aware they had the disease [97]. This is a common cause for both acute and chronic pelvic pain and may contribute to tubal factor infertility.

Etiology

Most commonly, the etiology is bacterial in origin. However, infection may also be due fungal, viral, and parasitic sources. Sexually transmitted organisms are implicated in many cases. *Neisseria gonorrheae* and *Chlamydia trachomatis* are most commonly implicated in disease. *C. trachomatis* and *N. gonorrheae* have been estimated to be present in approximately 60% and 30%, respectively, in cases of salpingitis, which may lead to PID. However, common microbes of the vaginal flora, such as anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*, have also been associated with PID [98, 99]. Notably, cytomegalovirus (CMV), *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium* have also been associated with some cases [100, 101]. Infection can be due to a single organism or coinfection with several different organisms.

Although causes attributed to sexually transmitted infections (STI) is common, other possible clinical settings for PID include postpartum endometritis, postabortal PID (e.g., following miscarriage or abortion), and immediately following IUD insertion [97]. In many cases, an organism is not isolated. Although many clinicians may be familiar with acute cases of PID, the acute form may evolve into a chronic form and result in CPP if unrecognized, untreated, or incompletely treated. The actual mechanism(s) by which CPP results from PID has not been well described. Not all women who suffer damage to the reproductive tract secondary to PID will develop chronic pain [1]. It is estimated that approximately 18–35% of all women with acute PID will develop CPP [102, 103]. Whether acute PID is treated with outpatient or inpatient regimens does not appear to significantly alter the odds of developing subsequent CPP [102].

Clinical Presentation

The accurate diagnosis of PID (acute or chronic) is challenging given the wide variety of symptoms and variable clinical presentation. Clinical diagnosis of symptomatic PID has a positive predictive value (PPV) for salpingitis of 65–90% compared with laparoscopy [99]. However, the PPV of a clinical diagnosis of acute PID depends on the characteristics of the population, with higher PPVs among sexually active young women (particularly adolescents), patients attending STD clinics, and patients residing in areas where the rates of gonorrhea or chlamydia are elevated [99].

In all clinical settings, no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of PID [99]. Possible symptoms include abdominopelvic pain, fever, vaginal discharge, dyspareunia, irregular menstrual bleeding, nausea, and vomiting secondary to abdominal pain. The differential diagnosis includes ectopic pregnancy, appendicitis, hemorrhagic ovarian cysts, leiomyoma degeneration, gastroenteritis, and acute enteritis. In the case of chronic PID, the more significant signs and symptoms of acute PID are not typically present [98]. Nonspecific symptoms may overlap with other gynecologic disorders (e.g., adenomyosis, endometriosis, uterine fibroids) and may not raise the clinical suspicion of the provider.

Diagnosis

When considering chronic PID and CPP, the clinician should realize that diagnostic guidelines published by the Centers for Disease Control and Prevention (CDC) have been established for the diagnosis and management of acute PID. Per 2010 CDC guidelines, a minimum of one of three clinical criteria are required for diagnosis [99]. These criteria include:

- Cervical motion tenderness OR
- Uterine tenderness OR
- Adnexal tenderness

Signs of lower-genital-tract inflammation (leukocytes in vaginal secretions, cervical exudates, or cervical friability), in addition to one of the three minimum criteria, increase the likelihood of the diagnosis [99]. One or more of the following additional criteria can be used to enhance the specificity of the minimum criteria and support a diagnosis of PID [99]:

- Oral temperature >101 °F (>38.3 °C)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of abundant numbers of WBC on saline microscopy of vaginal fluid
- Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
- Laboratory documentation of cervical infection with *N. gonorrheae* or *C. trachomatis*

Following the physical examination, the routine evaluation will include serum hCG (to exclude intrauterine or ectopic pregnancy), gonorrhea and chlamydia cervical cultures, CBC, wet mount (to detect concomitant infections such as bacterial vaginosis, trichomonas), and pelvic ultrasound (to exclude any additional gynecologic processes including tubo-ovarian abscess [TOA]). Pelvic MRI may be reserved for definitive characterization of suspected intra-abdominal or adnexal abscess. Typically, laparoscopy is reserved for cases where there is no clinical improvement following 48–72 h of inpatient medical therapy or when all etiologies for CPP have been excluded and the diagnosis of CPP due to chronic PID is uncertain.

The most specific criteria for diagnosing PID include [99]:

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal ultrasound or pelvic MRI imaging demonstrating thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
- Laparoscopic findings consistent with PID

Treatment

Due to the difficulty of diagnosis and the potential for distortion of the female reproductive tract (even by apparently mild or subclinical PID), clinicians should have a low threshold for the diagnosis and treatment of PID [99]. Both acute and chronic PID are treated similarly. Outpatient and inpatient regimens aim to provide broad-spectrum coverage which will treat both *N. gonorrheae* and *C. trachomatis*, and the most likely involved aerobic and anaerobic organisms. Per 2010 CDC guidelines, appropriate outpatient regimens include [99]:

Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

OR

Cefoxitin 2 g IM in a single dose and Probenecid, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

OR

Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

As a result of the emergence of quinolone-resistant *N. gonorrheae*, regimens that include a quinolone agent are no longer recommended for the treatment of PID. If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones (levofloxacin 500 mg orally once daily or ofloxacin 400 mg twice daily for 14 days) with or without metronidazole (500 mg orally twice daily for 14 days) can be considered if the community prevalence and individual risk for gonorrhea are low. If clinical improvement is not observed within 72 h of initiation of the above outpatient regimen, the

patient should be reevaluated to confirm the diagnosis and started on a parenteral regimen if PID is still suspected. Suggested parenteral regimens include [99]:

Recommended Parenteral Regimen A
Cefotetan 2 g IV every 12 h

OR

Cefoxitin 2 g IV every 6 h
PLUS
Doxycycline 100 mg orally or IV every 12 h

Recommended Parenteral Regimen B
Clindamycin 900 mg IV every 8 h
PLUS
Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 h. Single daily dosing (3–5 mg/kg) can be substituted

Alternative Parenteral Regimens
Ampicillin/sulbactam 3 g IV every 6 h
PLUS
Doxycycline 100 mg orally or IV every 12 h

Parenteral regimens should be continued until the patient has demonstrated clinical improvement. At that time, an oral regimen can be initiated within 24–48 h of clinical improvement and continued for a total duration of 14 days of therapy. In the case of TOA, at least 24 h of inpatient observation is recommended, and the addition of anaerobic coverage should be implemented in both inpatient and outpatient regimens. If there is no clinical improvement within 72 h of initiation of parenteral regimen, a reassessment of current regimen should be made to ensure adequate antimicrobial coverage. If the antibiotic regimen has been optimized, then additional surgical options such as laparoscopy or guided drainage of abscess (in the case of TOA) should be implemented.

In the special circumstance of pregnancy, the pregnant patient is not a candidate for outpatient treatment and should be admitted for inpatient parenteral therapy. The sexual partners of affected patients should also be treated and asked to abstain from intercourse until infection has been adequately treated. Testing for HIV, hepatitis B and C, and syphilis should also be offered to patients and their partners. If symptoms of CPP have not changed in character following optimal antibiotic treatment for PID and there is low suspicion for other common etiologies for CPP, an empiric approach with NSAIDs with or without hormonal suppression may be considered for initial medical therapy. If these measures prove unsuccessful, then diagnostic laparoscopy can be considered to investigate the etiology of CPP further.

Other Gynecologic Etiologies

Although clinicians considering gynecologic causes of CPP will emphasize the most common etiologies, there are several other less common disease processes which should be included in the comprehensive differential diagnosis.

Gynecologic Malignancy

One of the least suspected of gynecologic cancers, ovarian cancer, is the most fatal. The vast majority of ovarian cancer is not detected until an advanced stage due to lack of sensitive screening tests and nonspecific symptoms during early stages. Symptoms may include overlapping gynecologic, gastrointestinal, and urinary symptoms such as abdominal bloating, increase in abdominal girth, pelvic pain and pressure, constipation, indigestion, dyspareunia, urinary frequency, anorexia, nausea, vomiting, indigestion, and malaise. Additionally, cervical and fallopian tube cancers may present with typical gynecologic symptoms including irregular vaginal bleeding, abnormal vaginal discharge, and pelvic pain in the setting of a pelvic mass in the case of advanced disease.

Ovarian Remnant Syndrome

Patients with this condition may present with CPP following bilateral oophorectomy. Symptoms specific to this syndrome are related to the continued growth and ovulation of residual ovarian tissue due to exposure to endogenous gonadotropins. There may be cyclic pelvic pain and a pelvic mass detected on physical examination and imaging. In patients of premenopausal status, suspicion may be raised if the patient experiences monthly moliminal symptoms which are usually reported when at least one ovary has been left in situ.

Vaginal Cuff Prolapse

Pelvic organ prolapse is most commonly observed in the perimenopausal and postmenopausal periods. Some clinicians may assume that CPP in women who are postmenopausal or have had a hysterectomy cannot be due to a gynecologic origin. In the case of prior hysterectomy, the provider must ensure that the vaginal cuff is intact and exclude prolapse of intra-abdominal contents such as fallopian tubes, ovaries, and intestines through a defect in vaginal cuff mucosa. Common symptoms includes dyspareunia with deep penetration intermittent lower quadrant pain.

Tuberculous Salpingitis

Tuberculous salpingitis results from hematogenous and lymphatic dissemination of tuberculosis to the fallopian tube leading to granulomatous salpingitis. At the time of primary TB (Mycobacterium tuberculosis) infection, the disseminated microorganisms spread through the bloodstream to different organ systems remain dormant in latent foci. Tuberculous salpingitis is usually caused by reactivation of these dormant organisms, with drainage of tubal exudates into the endometrial cavity resulting in a granulomatous endometritis. PID may subsequently develop in an indolent fashion and become a cause of CPP. Other potential symptoms may include abdominopelvic pain, excessive purulent vaginal discharge, and irregular vaginal bleeding.

This source of CPP should be considered in those at high risk for prior primary TB infection (e.g., immigrants from Asia and Africa, public dwellings, immunosuppression) with current CPP of unclear etiology, and a prior history of PID. Staining of endometrial tissue (obtained from endometrial biopsy) for acid-fast bacilli is often negative. Culture isolation of the mycobacterium is the gold standard for diagnosis. The presence of typical granulomata in an endometrial biopsy or fallopian tube segments is sufficient for diagnosis in many cases.

Nongynecologic Etiologies of Chronic Pelvic Pain

Although the aim of this chapter is to discuss the diagnosis and management of gynecologic causes of CPP, this author would like to emphasize that there are several nongynecologic etiologies, which are commonly observed in the reproductive-aged women, and must be considered during evaluation. Although they are addressed in greater detail in this publication, common disorders such as interstitial cystitis, irritable bowel syndrome, and psychogenic factors will be briefly reviewed in this chapter in order to highlight their significant impact on CPP in women.

Interstitial Cystitis

Interstitial cystitis (IC) is a chronic inflammatory disorder of uncertain etiology of the urinary bladder, which may cause severe CPP, dysuria, urinary frequency and urgency, dyspareunia, as well as pelvic pressure. Given the close anatomical proximity of the urinary bladder with the female reproductive tract and vagina, patients with this disorder are often misdiagnosed with a gynecologic cause of CPP. Additionally, the symptoms may be mistakenly treated as recurrent urinary tract infection prior to correct diagnosis. Pelvic pain is reported in approximately 70% of women with IC and, in some cases, in the chief complaint during initial presentation [104]. Interestingly, it has been suggested that a range of 38–85% of women presenting to the gynecologist for CPP may actually have IC [105, 106].

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized predominately by chronic or intermittent abdominal pain associated with bowel dysfunction in the absence of an organic cause. Signature symptoms include a relapsing pattern of abdominopelvic pain with either constipation or diarrhea [1]. IBS is the most prevalent diagnosis in primary care practices and is one of the most common overall causes of CPP, occurring in an estimated 35% of women with CPP [107]. It has an increased prevalence in women with CPP compared to the general population [1]. IBS symptoms are found in approximately 50–80% of women with confirmed CPP [108, 109]. To this end, the provider should have a low threshold for referral of the patient with CPP to gastroenterology for further evaluation.

Given its coexistence with gynecologic causes of CPP, the clinician caring for women with chronic pain should be very familiar with this disorder. It is a diagnosis of exclusion after other etiologies have been ruled out. Specific diagnostic criteria for IBS are included in Rome III criteria [110].

Psychosomatic Factors

As mentioned previously, women with CPP have an increased risk of prior or current physical or sexual abuse. There is evidence to suggest that abuse may cause biophysical changes [2]. Specifically, a group of investigators have suggested that chronic or traumatic stimulation (especially in the pelvic and abdominal regions) may increase sensitivity to pain, result in persistent pain, and manifest as CPP with gynecologic and gastrointestinal symptoms in the absence of other etiologies [111, 112]. It is paramount to ensure that any woman with a history of abuse is not currently being abused, has an adequate support system, and is safe in her current surroundings [2].

Topics in Medical and Surgical Treatment

During the course of review of treatment options for common gynecologic disorders of CPP, it must be acknowledged that the efficacy of many medical and surgical interventions has not been comprehensively studied for all etiologies of this disorder. Due to the unpredictable nature of response to any proposed therapy, it is necessary that the clinician select the appropriate intervention with the most consistent track record for a specific underlying cause of CPP. As a result, the clinician should be familiar with the efficacy of a specific treatment choice as well as the associated limitations. Herein, pertinent topics for the medical and surgical treatment of CPP are discussed.

Medical Options

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Opioids

By virtue of their ability to attenuate endogenous prostaglandin synthesis, NSAIDs (COX-1 and COX-2 inhibitors) have proven to be an effective therapy for the prostaglandin-mediated events of the late luteal phase, menses, and dysmenorrhea [113]. Although there are no large scale randomized clinical trials to assess the efficacy of NSAIDs in the setting of CPP, these agents are widely used by clinicians and provide appropriate relief for many gynecologic causes of chronic pain (especially endometriosis, uterine leiomyomata, pelvic adhesive disease, and adenomyosis).

When additional analgesia is required above the limit of what NSAIDs can provide, opioids may also be considered for the treatment of CPP. There is evidence to suggest that opioids also provide significant analgesic effects but may not provide improvement in functional status [114]. As was the case of NSAIDs, there are no significant randomized trials available to comprehensively demonstrate the efficacy of opioids for CPP. The clinician should also lend special attention to any medical contraindications to NSAIDs (e.g., current or prior active peptic ulcer disease, gastritis, renal insufficiency) and any concerns with opioid cross-reactivity with any prescribed sedative, as well as the potential risk of addiction with long-term use.

Hormonal Therapy

Combination oral contraceptive pills (OCPs) contain bioactive synthetic estradiol and progestins which suppress pituitary gonadotropins, prevent ovulation, minimize menstrual flow and uterine contractile activity, and attenuate prostaglandin synthesis in order to minimize pelvic discomfort during menses. This class of medication is the mainstay of treatment for dysmenorrhea and is used widely for many sources of CPP which are primarily gynecologic in origin or are exacerbated during a specific phase of the menstrual cycle. In tandem with NSAIDs, OCPs are recommended as first-line therapy for endometriosis-associated pain [115]. One clinical trial demonstrated that OCPs and GnRH agonist (goserelin) provided similar relief of CPP and dyspareunia, while the GnRH agonists provided superior relief for dysmenorrhea [116]. These two agents in addition to GnRH agonists may be considered primarily for CPP due to endometriosis, while there is limited data studying their efficacy with other gynecologic disorders. Additionally, second- and third-line medications such as danazol levonorgestrel IUD and aromatase inhibitors have also been utilized with endometriosis-associated pain but have been limited in use due to their respective side effect profiles.

Oral progestins are another class of hormonal therapy, which has been mainly studied in the setting of endometriosis-associated CPP as well. Specifically, oral medroxyprogesterone acetate (30–100 mg daily) has been shown to be effective for CPP due to both endometriosis and pelvic congestion syndrome [2, 117, 118].

Alternative Medical Therapy

Nontraditional treatment options for CPP include acupuncture, biofeedback, transcutaneous nerve stimulation, and herbal and nutritional supplements. Although widely used by many practitioners, further comprehensive investigation is needed prior to the recommendation of these options as effective treatments for nonmenstrual pelvic pain.

Surgical Options

Hysterectomy

In the setting of pelvic pain, the uterus is typically implicated as the primary gynecologic source of symptoms. Although approximately 12% of the 600,000 annual hysterectomies are performed for the primary indication of CPP, more than half of the etiologies attributed to CPP may not be gynecologic in origin [10, 11, 117]. As a result, the role of hysterectomy in the treatment of idiopathic CPP remains controversial. There is convincing evidence that patients undergoing hysterectomy for benign nonpainful disorders have excellent outcomes [117]. However, it is not as clear that this surgical option provides adequate improvement and resolution of CPP symptoms for all patients.

The quintessential question with regard to hysterectomy and CPP has been: "Which patients with CPP will ultimately benefit from hysterectomy?" This has been a difficult question to answer due significant limitations of study designs in the literature. A notable early publication demonstrated that 78% of women with CPP had significant improvement of symptoms from 12 to 64 months following hysterectomy, while 22% reported continued symptoms [118]. Surprisingly, continued pain was also observed in those who were thought to have clinical and histological findings of uterine disease [117, 118]. A subsequent study reported similar results and identified that subsets of women who were less than 30 years of age, uninsured, had Medicaid insurance coverage, were without identifiable pathology at the time of surgery, and had a history of pelvic inflammatory disease continued to experience postoperative pain more than 1 year following hysterectomy [117, 119].

Additional factors influencing outcomes were related to psychosocial factors. Specifically, depression and anxiety were investigated as predictive factors of persistent postoperative pain. Hartmann and colleagues reported that women with preoperative CPP and depression were three to five times more likely to have continued pelvic pain and dyspareunia compared to controls [120]. The authors concluded that "women with pelvic pain and/or depression fared less well 24 months after hysterectomy than women who have either disorder alone or together" [117, 119]. Even more surprising were the findings of a Danish nationwide survey study which confirmed the results of Hartmann et al. but also reported an increase in pain in other subsets of patients following surgery [121].

When reviewing studies that have examined the effect of hysterectomy on CPP, it is evident that the risk of treatment failure with hysterectomy is much greater in women with preoperative pain. Consequently, hysterectomy may not always be successful in reducing and/or eliminating symptoms. A primary explanation for this observation may be that an incorrect preoperative diagnosis for CPP has been made. That is, a nongynecologic cause of pain may have been overlooked and treated incorrectly with a surgical intervention aimed to treat a gynecologic source. Additionally, the underlying mechanisms of certain subtypes of CPP may alter the innervation of abdominal/pelvic viscera and musculature in such a manner that removal of the uterus may not be sufficient to improve symptoms [117]. With these facts in mind, consideration of hysterectomy in a woman with CPP should be based upon a reasonable certainty for a gynecologic etiology, exclusion of occult nongynecologic and psychosocial factors, and a focused utilization of medical therapy initially. Most importantly, the option of hysterectomy should include an open dialogue between clinician and patient, with an emphasis on potential failure rates as high as 40%, a 5% risk of worsening symptoms postoperatively, and an open disclosure that this option will not always provide a definitive cure for CPP.

Presacral Neurectomy and Uterosacral Nerve Ablation

Investigators have found that presacral neurectomy (surgical resection of the hypogastric plexus) provides pain relief for mainly central (midline) dysmenorrhea in women with and without endometriosis. No significant benefit has been observed for dyspareunia and nonmenstrual pain [122, 123]. There is no available evidence in the literature to support the role of uterosacral nerve ablation (transection of uterosacral ligaments at their uterine insertions) for the treatment of dysmenorrhea, dyspareunia, or nonmenstrual CPP.

Case-Based Presentation

Chief Complaint

Thirty-four-year-old gravida 3, para 3 woman with last menstrual period 15 days ago who presents with 12 months of pelvic pain, menorrhagia, and intermittent diarrhea.

History

The history of present illness is remarkable for midline central pelvic pain, which is constant in duration, sharp in nature, and has no radiation. She rates her pain as a

four out of ten at baseline. Two days prior to expected menses, she notes progressively worsening pelvic pain with associated diarrhea and suprapubic pain. All stated symptoms were most severe on cycle day (CD) 1 and returned to baseline at the resolution of menses on CD 5. She notes intermittent constipation and diarrhea throughout the remainder of her cycle. She otherwise denies hematuria, dysuria, dyschezia, melena, dyspareunia, vaginal discharge, or any musculoskeletal complaints. She notes slightly increased menstrual flow (requiring six pads per day at peak [was four pads per day at peak previously]).

She is previously healthy and has an unremarkable past medical and surgical history. She is not taking any medications and has no known drug allergies.

She notes normal developmental (growth, menarche, secondary sex characteristics) milestones, and denies any prior sexually transmitted diseases, abnormal PAP smears, and prior PID, and has had only one lifetime sexual partner. She has had three full-term uncomplicated normal spontaneous vaginal deliveries. She has normal menstrual intervals of every 28 days. Menses last for 5 days.

She notes moderate dysmenorrhea.

She is employed as registered nurse in the cardiac care intensive care unit. She has been married for 10 years and has three living children. She is a social drinker and denies the use of tobacco or recreational drugs. She denies any prior or current symptoms of depression or anxiety. She also denies any previous or current history of physical or sexual abuse.

Physical Examination

The focused physical examination is notable for an unremarkable abdominal examination with the exception of mild midpelvic tenderness with deep palpation. Speculum examination was unremarkable. Bimanual examination was notable for a mildly enlarged uterus (10–12 weeks size), mildly tender uterine fundus, and tender left adnexa. No cervical motion tenderness and no pelvic masses were appreciated. Rectovaginal examination was unremarkable.

Diagnostic Testing

Cervical culture for gonorrhea and chlamydia was negative. Urine culture and sensitivity was unremarkable. Complete blood count, thyroid-stimulating hormone (TSH), and prolactin assays were within normal limits. Pelvic ultrasound demonstrated a retroverted uterus $12 \times 10 \times 8$ cm, with homogeneous endometrial lining of 8 mm. The myometrium revealed heterogeneous echogenic foci. Right and left ovaries were of normal size. A 20-mm complex cyst was observed in the left ovary, consistent with a hemorrhagic cyst. Trace simple free fluid was observed in the posterior cul-de-sac.

Discussion

In this clinical scenario, the key to directed treatment is based upon formulation of an appropriate differential diagnosis. Given her initial complaints of pelvic pain, menorrhagia, and diarrhea, the differential diagnosis encompasses gynecologic and nongynecologic etiologies. With an initial focus on gynecologic etiologies, the history and physical examination revealed bleeding and pain symptoms with an emphasis on constant pain that is exacerbated during the menstrual phase. Endometriosis, adenomyosis, and uterine leiomyomata seem most likely, while pelvic adhesive disease, chronic PID, and pelvic congestion syndrome seem least likely. Given her intermittent symptoms of bowel dysfunction prior to menses and throughout the menstrual cycle, a significant nongynecologic etiology, irritable bowel syndrome, is a consideration for the differential diagnosis as well. Due to a lack of significant urinary symptoms, interstitial cystitis (IC) seems to be a less likely cause.

Based upon physical examination findings, many symptoms were reproduced within the female reproductive tract. As a result, initial testing was directed toward imaging of the uterus with pelvic ultrasound, excluding any infectious causes of disease, and ensuring that anemia was not present based upon her perceived increase in menstrual flow. Although it may seem that the most likely causes of her symptoms may be gynecologic in origin, the clinician is obligated to further investigate irritable bowel syndrome and other gastrointestinal sources as contributory factors in this clinical circumstance.

Management of this patient initially involves referral to a gastroenterologist to assess for possible irritable bowel syndrome or any other gastrointestinal etiologies. From a gynecologic standpoint, initial treatment would be focused on minimizing the exacerbation of symptoms during menses, reducing menstrual flow, and reducing the degree of nonmenstrual pain. In this situation, adenomyosis and endometriosis seem to be the most likely etiology for symptoms based upon the history, exam, and testing. As a result, NSAIDs and OCPs would be reasonable for first-line medical therapy. A continuous OCP regimen with placebo every 3–4 months may be ideal to minimize exacerbation during menses. If symptoms do not improve following 3–6 months, a reassessment is warranted. If no additional factors are suspected, second-line medical options (e.g., progestins, GnRH agonists) may be considered. If the side effects of second-line options are unacceptable or these options are not successful, then diagnostic laparoscopy may be offered to investigate and possibly treat other gynecologic etiologies such as endometriosis.

As a final point of emphasis for a common clinical scenario as this, the initial diagnosis for the source of CPP may not be the correct diagnosis and/or there may be more than one source of pain. If response to therapy is unsuccessful or less than expected, reassessment of the initial diagnosis must be initiated and alternative CPP etiologies should be considered. Even if gynecologic symptoms are obvious in the setting of CPP, nongynecologic sources may still be contributory to the overall clinical picture.

Conclusions

Chronic pelvic pain (CPP) is one of the most prevalent disorders of women in primary care and specialty medical practice. It is a significant contemporary health issue for many women and causes severe disability in all demographic groups. Due to a lack of consensus in the definition for CPP and a diversity of symptoms demonstrated by many women with this disorder, diagnosis and management can be complex and challenging. Because CPP may be caused by conditions of both gynecologic and nongynecologic etiologies, simultaneous treatment of more than one disorder is common. Although CPP is more prevalent in women than men, it is estimated that common etiologies of gynecologic origin (e.g., endometriosis, leiomyomata, adenomyosis, pelvic adhesive disease, pelvic congestion syndrome, and chronic pelvic inflammatory disease) may only account for approximately half of all cases. Because of the clinical overlap of gynecologic, gastrointestinal, urological, and musculoskeletal disorders, a comprehensive history and physical examination is necessary for precise diagnosis and effective treatment. With regard to gynecologic causes, the aim of medical therapy is to minimize symptoms by attenuation of the prostaglandin-mediated pathways of pain during the menstrual cycle, suppress ovulation, and reduce the exacerbation of symptoms during menses. Due to the complex pathogenesis of CPP, surgical treatment options may not offer any greater benefit for improvement of symptoms compared to medical therapy. Treatment of this disorder is not always curative. However, pain specific therapy may improve symptoms so that the patient may resume normal life activities and secure a better quality of life after several years of possible misdiagnosis, frustration, and disability. Ultimately, a multidisciplinary approach for the woman with CPP will provide the most comprehensive and sensitive solution for this challenging disorder.

Patient Resources

Pelvic Pain

International Pelvic Pain Society (http://pelvicpain.org/)

Endometriosis

World Endometriosis Society (http://endometriosis.ca/)
Endometriosis Foundation of America (http://www.endofound.org)
American Society for Reproductive Medicine (http://www.asrm.org/)

Fibroids

National Uterine Fibroids Foundation (http://www.nuff.org/)

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Chapter 5
Pelvic Floor Muscle Pain and Dysfunction

Sharon Silveira and Samantha J. Pulliam

Introduction

The pelvic floor provides anatomic support and coordinates the essential functions of defecation, micturition, and reproduction. The nerves and muscles of the pelvic floor act as an integrated unit, and when a component is compromised, dysfunction and pain can result. One type of dysfunction is the development of hypertonic muscles. The increased tone can lead to multiple problems seen by physicians including bladder or bowel pain, elimination disorders, vaginismus, vulvodynia, as well as chronic pelvic pain.

Chronic pelvic pain (CPP) has been reported to affect 4–25% of women [1–4]. Significant numbers of these women (25–40%) will have a negative laparoscopy leaving a pelvic floor hypertrophic disorder high on the differential [5]. Myofascial pelvic pain (MFPP) is a hypertrophic pain disorder characterized by the development of one or more trigger points (TP) within the pelvic floor muscles. A trigger point is a hypersensitive area within a taut band of skeletal muscle. This area can cause local pain and over time can lead to regional and diffuse pelvic pain as well as visceral dysfunction.

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As there is a great deal of symptom overlap between pelvic pain syndromes, it can often be difficult to determine if the patient's symptoms originate from a myofascial etiology or if they are secondary to another pain disorder. In fact, it is often not one or the other, as studies have shown that 70% of women with bladder pain syndrome/interstitial cystitis have a hypertrophic disorder [6] with 87% having levator pain [7]. Whether a primary or secondary cause of pain, MFPP is an important component of pelvic floor dysfunction and must be addressed when evaluating and treating a patient who presents with urinary, defecatory, or vaginal symptoms as well as those patients with a diagnosis of CPP.

Pathophysiology

The levator ani muscles are the primary support for the pelvic organs. The levators are comprised of three muscles: the iliococcygeus, pubococcygeus, and puborectalis, and together with the coccygeus and endopelvic fascia form the pelvic floor. The iliococcygeus originates from the ischial spine and from the posterior part of the arcus tendineus and inserts on the coccyx and anococcygeal raphé. The pubococcygeus originates from the symphysis pubis and the anterior part of the arcus tendineus and travels horizontally and posteriorly where it inserts on the coccyx and sacrum. The puborectalis arises from the symphysis pubis and superior fascia and meets to form a sling around the lower part of the rectum.

The pubococcygeus and iliococcygeus along with the anterior vaginal wall support the bladder and bladder neck. The puborectalis forms a sling around the lower part of the rectum and in conjunction with relaxation of the internal and external anal sphincters controls defecation.

Innervation to the levator ani muscles is predominantly by direct branches of S3–S4 with minimal, if any, innervation from the pudendal nerve [8]. The pudendal nerve provides the main sensory innervation to the external anal sphincter, perianal skin, clitoris, ischiocavernosus, bulbocavernosus (vs. bulbospongiosus), superficial transverse perineal muscles, striated urethral sphincter, and labial skin [8]. Visceral information is carried by afferent nerves to the dorsal columns of the spinal cord by the sympathetic (hypogastric, T10–L2) and parasympathetic (pelvic, S2–S4) nerves (see Chap. 2) [9].

Myofascial pelvic pain is felt to originate from an abnormal response to muscle fiber trauma causing peripheral and then central sensitization. Inflammatory mediators including bradykinin, serotonin, prostaglandins, adenosine triphosphate, and histamine are locally released when a muscle is injured [10]. Over time, the muscle nociceptors become conditioned to the stimulus, and a lower response threshold to inflammatory mediators and mechanical stimulation results [11]. This leads to muscle hyperalgesia and is referred to as peripheral or primary sensitization.

Continued input from the afferents of an injured or painful muscle leads to neuroplastic changes in the dorsal spinal cord, a process mediated by the release of glutamate, *N*-methyl-D-aspartate, and substance P. This process is termed central

sensitization and results in amplified pain to both noxious and non-noxious stimuli as well as secondary hyperalgesia where pain is also perceived in tissue outside the area innervated by the injured nerve [5, 9, 12]. Studies in animals have shown that the sensitization process is extended not only across multiple adjacent spinal segments but also to the contralateral dorsal horn leading to the perception of pain in non-injured tissue [12].

Visceral hyperalgesia is another contributor to CPP. One explanation is extravasation of inflammatory modulators from inflamed or irritated viscera to its corresponding myotomes and/or dermatomes. In addition, somatic and visceral afferents may lose specificity at the level of the dorsal horn via shared synapses. This has been termed viscerosomatic convergence, and while it allows for the coordination of micturition and defecation, it can also lead to viscerosomatic sensitization and muscular hyperalgesia. This can result in a hypertonic contractile state and the development of coexisting pelvic pain disorders. This is, therefore, the most likely proposed mechanism by which patients with urologic pain disorders are found to have coexistent hypertrophic muscle pain disorders [9].

As discussed earlier, a trigger point is a hypersensitive area within a taut band of skeletal muscle. Trigger points begin with muscle fiber injury but may evolve through the above processes of peripheral and central sensitization to create local, regional, and diffuse pain, as well as the generation of new TPs. An active TP generates spontaneous pain to local muscle ischemia as well as inflammatory mediators and produces a twitching response when palpated. Latent TPs produce pain with pressure or muscle activity and can be activated by systemic or mechanical factors including stress, anxiety, sleep disorders, hypothyroidism, hypokalemia, malnutrition, posture, holding of urination, a urinary tract infection, or herpes activation [9, 10, 13].

Physical, mechanical, systemic, and psychological factors have been associated with the development of TPs [13]. Physical factors include injury to the pelvic floor nerves and muscles at the time of childbirth or surgery. Studies have shown that the act of or attempt at a vaginal birth changes the pudendal nerve conduction pattern [14]. Other studies have shown levator ani defects in parous women with chronic pelvic pain, including avulsion of the pubococcygeus from its origin at the pubis or at the arcus tendineus, as well as a decrease in muscle volume, density, and structure [14, 15]. The associated surgical procedures contributing to MFPP include sacrospinous ligament suspensions and prolapse repair with or without mesh, where sutures are anchored into the levator muscles [10]. Mechanical and structural factors involved include abnormal posture, leg length discrepancy, gait disturbances, sacroiliac joint dysfunction, and diastasis recti, all of which can trigger an asymmetric use of the levators [10, 13]. Systemic factors such as subclinical hypothyroidism, nutritional inadequacies, chronic allergies, and impaired sleep have also been linked to the development and activation of TPs [13]. A history of sexual, physical, and emotional abuse at a young age or as part of a domestic relationship, as well as anxiety and insomnia, is also common in those affected by MFPP [6, 13, 16]. While depression is frequently seen in this population, it is often thought to be a result of chronic pain rather than the primary cause [13].

As a primary disorder, MFPP can cause visceral dysfunction such as urinary incontinence or constipation. This occurs as the muscles containing trigger points become shorter and weaker and are no longer able to quickly respond to a stimulus due to early fatigue and delayed relaxation [9]. Through a similar injury cycle, MFPP also develops secondary to pelvic visceral dysfunction or another pelvic pain disorder. Interstitial cystitis/bladder pain syndrome, idiopathic urinary retention, irritable bowel syndrome, constipation, levator ani syndrome, proctalgia fugax, vulvodynia, vulvar vestibulitis, vaginismus, and endometriosis can all lead to the development of MFPP through central sensitization and the neuropathic visceromuscular hyperalgesia reflex as described earlier [1, 5, 10].

Assessment

When a patient presents with pelvic pain or dysfunction, the most important part of the workup is the history and physical exam. The clinician should ask the patient to discuss the location and quality of the pain. With MFPP, patients often have a difficult time localizing the pain. The pain may be described as originating in the lower abdomen, ovary, suprapubic, vaginal, or rectal regions. They often characterize the pain as achy, throbbing, or pressure-like in quality. Myofascial pain can radiate to the hip or back and is frequently noted to get worse over the course of the day or specifically after intercourse or with elimination of the bowel or bladder [5]. This pain is different from cutaneous pain which is more easily localized, superficial, and characterized as burning or sharp [11].

Associated symptoms should be thoroughly investigated including questions about bowel, bladder, and sexual function. Clinicians should inquire about urinary frequency, urgency, retention, and hesitancy; post-void pain; urethral pain; bowel habits; diarrhea; constipation; painful defecation; sharp rectal pain; vulvar pain, burning, irritation, and rawness; dysmenorrhea; dyspareunia; postcoital pain; clitoral pain; and pain with orgasm. While these symptoms can be present with MFPP, they can also be part of another pelvic pain disorder. It can be helpful to try to identify which symptoms came first.

Clinicians should spend time identifying precipitating factors. This includes a detailed obstetric history including the length of the second stage of labor, whether a forceps or a vacuum was used, whether an episiotomy was made, and the extent of any perineal or vaginal lacerations. A thorough medical, surgical, and psychiatric history should then be obtained. It is important to specifically ask about any childhood elimination disorders as many studies have shown a link between symptoms such as recurrent urinary tract infections and enuresis, and interstitial cystitis, overactive bladder, as well as other pelvic floor hypertonic disorders [10, 13, 17]. If the patient has had abdominal, pelvic, or back surgery, getting a clear sense of the indication and outcome is essential. As part of the social history, the physician should ask specifically about abuse including questions about childhood and domestic abuse. Daily activities such as work, recreational interests, and life stressors should

also be discussed. If the patient has seen other healthcare providers, medications and treatments tried in the past must be reviewed.

Time can be saved by having the patient answer many of the above questions on an intake questionnaire. In addition, validated questionnaires such as the Pelvic Floor Distress Inventory, Pelvic Floor Impact, and Pelvic Pain and Urgency/Frequency Questionnaires can be used [13, 18]. Another simple way to assess voiding and defecatory symptoms as well as pelvic pain triggers is to ask the patient to keep a symptom diary.

The physical exam begins during the history by observing the patient's posture and affect. Patients with pelvic pain will frequently lean to one side while sitting and/or sit on their leg in order to alleviate pressure on the pelvic floor muscles [13]. The clinician should examine the patient, if possible, in standing and walking to again assess stance and posture and ascertain if there is any gait disturbance.

The pelvic exam should begin with observation. In the dorsal lithotomy position, the physician should evaluate the external genitalia and look for asymmetry or dermatologic abnormalities. The patient should then perform a Kegel squeeze (to facilitate the patient's understanding of this maneuver, the patient can be asked to hold urine or flatus). Hypertonic muscles are contracted at rest and will be unable to squeeze effectively and then relax in a stepwise manner or reflexively tighten again after contraction. These muscles may also be seen to fasciculate during this maneuver [5].

A cotton swab test is performed next to evaluate for vulvodynia. During this test, the vestibule is touched with a lubricated cotton swab at 2, 4, 6, 8, and 10 o'clock and the patient is asked to rate the pain on a visual analog scale.

The clinician then places a lubricated single finger into the vagina and asks the patient to perform another Kegel squeeze to assess for strength, tone, and tenderness. In patients with hypertonic disorders, the vagina often palpates like a "V" with the levators forming a shelf instead of a smooth cylinder [10] with incomplete relaxation following the Kegel. The superficial muscles including the ischiocavernosus, bulbocavernosus, and superficial transverse should then be palpated and the tone assessed. Pressure is next applied to the pubococcygeus and iliococcygeus muscles bilaterally, and the extent of contraction, degree of relaxation, and magnitude of tenderness are evaluated. Attention is paid to any trigger points, 3–6 mm exquisitely tender nodules that reproduce the patient's local and referred pain. The patient should also be asked to voice any visceral symptoms, such as the urge to urinate or defecate, that are stimulated during the exam. Palpation should conclude with an exam of the bladder base, cul-de-sacs, cervix, uterus, and adnexa [13, 16, 19].

Speculum examination, if indicated, should be deferred until the aforementioned parts of the pelvic examination have been completed, as placement of the speculum can trigger intense pain and can make a thorough evaluation challenging. With the speculum exam, the physician should look for atrophic vaginitis and perform a vaginal pH test, wet prep, and vaginal/cervical cultures if indicated [13, 16].

Finally, a rectal exam is performed. The tone of the external sphincter and puborectalis are evaluated as well as the anorectal angle (normal = 90°, <90° = hypertonic) and the position (normal = 30° flexion) and flexibility of the coccyx [19].

While there are no specific labs or imaging studies to diagnose MFPP, additional tests can be helpful in certain circumstances. Objective evidence of hypertonic dysfunction can be obtained with surface EMG with patients showing at least three out of five of the following findings: elevated and unstable resting baseline activity, poor recovery, poor post-contraction relaxation, spasm with sustained contractions, and reduced strength [8]. If levator trauma is suspected as a precipitating and/or contributing factor, three- and four-dimensional sonographic and magnetic resonance imaging have both been shown to offer precise imaging of the pelvic soft tissues, revealing the presence and extent of any levator defects [14, 15]. A CBC; chem7; ESR; vitamin C, D, B-1, B-6, B-12; folic acid; and/or thyroid assay may be warranted if a predisposing factor such as hypothyroidism, hypoglycemia, or vitamin insufficiency is suspected [13].

If a urologic or gastrointestinal disorder is suspected either as the primary diagnosis or as a precipitating factor to the development of MFPP, the clinician should consider additional tests related to the suspected disorder. Possible evaluations to consider include urinalysis, urine culture, urine cytology, cystoscopy with hydrodistention, intravesical potassium sensitivity test, renal radiography, urodynamics, endoanal ultrasound, evacuation proctography, MR defecography, anorectal manometry, and anal sphincter EMGs [1, 5, 20, 21].

Treatment

Treatment of myofascial pelvic pain often involves a multispecialty and multidisciplinary approach. As MFPP is often associated with other diagnoses such as irritable bowel syndrome [12, 22], endometriosis [23, 24], depression [24], constipation [25], interstitial cystitis [7], and chronic urinary tract infections [26], it is critical to treat these concomitant, possibly exacerbating, or inciting problems. Specific pharmacological or surgical intervention may be necessary in some cases. Interstitial cystitis may be addressed with oral medications such as pentosan polysulfate sodium, which coats the damaged cellular lining of the bladder, or with bladder instillations of dimethyl sulfoxide or heparin. Suppressive or preventive antibiotics for recurrent urinary tract infection may be considered for short-term (several months) use. Constipation should be evaluated carefully to determine its etiology and treated aggressively.

Neurogenic pain, or allodynia, may be treated with a number of medications. Tricyclic antidepressants have been shown to decrease neuropathic pain in many regions of the body (torticollis, migraine, etc.) and may have some effectiveness in the area of MFPP as well [27]. Antiepileptic drugs such as gabapentin or pregabalin have also shown efficacy [28]. One small, randomized study in Austria [29] demonstrated improvement in pain scores for patients using amitriptyline (up to 150 mg) and gabapentin (up to 3,600 mg), with superior pain improvement in patients using gabapentin alone or gabapentin plus amitriptyline. Patients should be aware of

potential adverse effects of these medications including somnolence and weight gain. Tricyclics should be gradually increased over several weeks, and patients should be counseled that effectiveness may not manifest until several weeks of use.

Pelvic floor physical therapy (see Chap. 14) is a mainstay for the treatment of myofascial pelvic pain. Techniques such as Thiele's massage, targeting specific muscles in the pelvis, have been shown to be effective [30–33]. Biofeedback and bladder retraining have also been identified as useful tools in therapy for myofascial pain. Markwell [34] demonstrated an 87% response rate to physical therapy for the treatment of levator ani syndrome and descending perineum syndrome. Oyama [30] showed a significant improvement in symptoms of chronic pelvic pain and interstitial cystitis after transvaginal manual therapy, lasting over 4 months. Electromyographic biofeedback of pelvic floor musculature has been associated with a subjective decrease in pain by 68% in patients with vulvar vestibulitis. Weiss [31] demonstrated an improvement in urgency frequency syndrome symptoms in patients with interstitial cystitis after 8–12 weeks of manual physical therapy.

Trigger point injections into pelvic floor muscles have also been shown to be helpful in pain relief. Fitzgerald [35] describes injection of up to 30 mL of 0.25% bupivacaine into PFM using a needle and trumpet kit designed for administering pudendal nerve blocks. One purpose of these injections is to facilitate more intensive manual physical therapy, which may not be otherwise possible due to patient discomfort. Some patients find increased PFM pain within days of injection or manual therapy, due to increased range of motion of these muscles during therapy. PFM injections have also been used in association with at-home PFM exercises, resulting in a 50% decrease in pain in 72% of participants [36].

Botulinum toxin A (BoNT/A) has been used to reduce chronic pelvic pain and pelvic floor muscle spasm. The effects of BoNT/A are thought to be caused by inhibition of acetylcholine, a neurotransmitter present at the neuromuscular junction in striated muscle. BoNT/A may also work by decreasing release of glutamate and substance P, inhibiting sensitization of nociceptive fibers [37]. Multiple case series, reporting pelvic floor muscle injections in over 100 women, suggest that botulinum toxin A may be useful in addressing pelvic floor muscle spasm. Dosing for these series ranged from 20 to 400 units BoNT/A [38, 39]. In a small, double-blinded, randomized, placebo-controlled trial [40], Abbot demonstrated a significant decrease in non-menstrual pain, dyspareunia, and pelvic floor pressure. However, only pelvic floor pressure was significantly reduced versus placebo, and though both groups experienced diminished pain, the intergroup differences were not statistically significant.

Sacral neuromodulation (SNM) is another option for the treatment of MFPP. SNM involves the stimulation of the afferent S2–3 nerve roots. An implantable device (Interstim, Medtronic, Inc.), providing unilateral nerve root stimulation, has been FDA approved for use in the treatment of refractory, nonobstructive urinary retention, urinary frequency, urgency, and urge incontinence. Although not FDA approved for the treatment of interstitial cystitis (IC) or pelvic pain, some studies suggest that SNM may be useful for these conditions. Peters [41] describes greater

than 50% improvement in pain in over 50% of IC patients after implantation of a sacral neuromodulation device. Zabhihi et al. [42] note a 40% improvement in visual analog scale pain scores among patients with IC and chronic pelvic pain, although this study reported only short-term (6 months) results. The mechanism of action for pain relief is uncertain, though one explanation may be the disruption of transmission of pain signals to the brain by stimulating activity in large-diameter A-beta fibers [43].

Case-Based Discussion

TV is a 31-year-old G4P4 otherwise healthy woman who underwent vaginal hysterectomy with sacrospinous ligament suspension for treatment of pelvic organ prolapse. Immediately following the procedure, she experienced constant right-sided pelvic pain, described as a deep, sharp pain rated 7/10 in severity and worsened with urination and bowel movements. She was referred to pelvic floor physical therapy but did not tolerate intravaginal manual therapy due to pain. Two months later, she underwent examination under anesthesia with pelvic floor muscle trigger point injections (0.5% Marcaine) and excision of vaginal apex granulation tissue. This provided minimal relief.

She was subsequently evaluated by our practice. Examination revealed a short, tight tender puborectalis muscle with 10/10 pain elicited by palpation. She was prescribed gabapentin at a starting dose of 100 mg TID but was unable to start due to lack of insurance coverage. Following the administration of vaginal lidocaine (1%) jelly, she underwent pelvic floor trigger point injections. Using a combination of intravaginal topical lidocaine and twice-monthly trigger point injections, she was able to tolerate intravaginal physical therapy. Although physical therapy was uncomfortable, this responded partially to cyclobenzaprine. She underwent a trial of amitriptyline but found it too sedating. Gabapentin 100 mg TID was finally initiated following an appeal to her insurance company. With this regimen, she was able to tolerate weekly physical therapy. Within 3 months, she reported improvements in pain and function. However, she continued to experience exacerbations of pain, particularly associated with intercourse.

She then underwent laparoscopic surgery for removal of the uterosacral ligament suture and lysis of adhesions (the right ovary was densely adherent to the vaginal cuff). Initially, she experienced pain relief but within months was experiencing debilitating painful episodes described as "muscle spasms" that prevented driving or walking. She underwent further trigger point injections, both intravaginal and involving the muscles of the hip and lumbar spine areas. She continued with physical therapy.

Ultimately, botulinum toxin injection into her levator ani muscle was performed. Eighty units of botulinum toxin A were injected into the levator ani, bilaterally, at eight separate injection sites. One-month follow-up revealed near-complete resolution of pain, with no evidence of urinary retention or fecal incontinence.

Conclusion

Pelvic floor muscle disorders represent a challenging diagnostic and treatment dilemma for many healthcare providers and the patients they care for. In part, this may be due to limited awareness and understanding of the musculoskeletal function of pelvic floor muscles. Many clinicians are well trained in the assessment and treatment of familiar problems identified within their specialty, such as endometriosis, interstitial cystitis, or irritable bowel syndrome, but less familiar with the assessment and treatment of myofascial pelvic pain. A more complete understanding of this pain syndrome could contribute to a more complete treatment of chronic pelvic pain and associated conditions.

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Chapter 6
Vulvodynia

Jennifer Gunter

Chronic vulvar pain affects 3–10% of women with a similar prevalence among white and African-American women [1–4]. Previously termed vulvodynia and vestibulitis, chronic vulvar pain syndromes have been reclassified by the International Society for the Study of Vulvovaginal Disease (ISSVD) as spontaneous or provoked pain with further subtyping based on location, i.e., generalized versus localized (Table 6.1) [5, 6]. Dyspareunia, which affects up to 22% of women, is an almost universal finding among women with vulvodynia and is classified as primary (present from first attempt at coitus or tampons) or secondary (developing sometime after pain-free intercourse has been established) [7].

Pathophysiology

Vulvodynia has characteristics of both neuropathic pain and nociceptive pain. Thermal adjectives, such as hot, burning, or scalding, typically associated with neuropathic pain are most commonly used to describe the pain of vulvodynia [8–11]. Allodynia (pain from a stimulus that should not normally be painful) and hyperalgesia (increased sensitivity to normally painful stimuli) are part of the diagnostic criteria for vulvodynia and are important findings associated with neuropathic pain [5, 9]. However, some women also describe sharp and/or tearing pain, especially with intercourse, which is more characteristic of nociceptive pain [9, 11].

Neuropathic pain is the result of injury to the peripheral or central nervous system. After peripheral nerve injury, a greater loss of small-diameter C-fibers than of large-diameter A-beta fibers, normally responsible for light touch, has been demonstrated in animal models. Subsequently, the surviving A-beta fibers sprout new branches

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Table 6.1 2003 ISSVD classification of vulvodynia

Generalized pain	Localized pain (vestibule, clitoris, etc.)
Provoked by touch	Provoked by touch
Unprovoked (spontaneous)	Unprovoked (spontaneous)
Mixed	Mixed

in the substantia gelatinosa (lamina II) of the spinal cord, making connections to second-order neurons vacated by the lost C-fibers [12, 14]. As a result, A-beta fibers become capable of transmitting painful stimuli, taking on a primary nociceptive role. This phenomenon is believed to be an important contributor to allodynia [12]. Other changes in the central nervous system contribute to the genesis and maintenance of neuropathic pain, for example, increased release of inflammatory neuropeptides and neurotransmitters, abnormal excitatory changes and synapsing of wide dynamic range (WDR) neurons, activation of *n*-methyl-D-aspartate receptors, and alteration of gene expression [6, 10, 12–14].

Nociceptive pain is secondary to stimulation and/or response of nociceptors, undifferentiated nerve endings of myelinated A-delta and unmyelinated C-fibers. Nociceptor sensitization, meaning increased sensitivity to excitatory neurotransmitters resulting in depolarization at a lower threshold or even spontaneous firing, has been identified in women with localized vestibulodynia, although there are no studies evaluating women with generalized pain [15]. Among women with localized provoked vestibulodynia, an increased proliferation of peripheral nerve fibers and vanilloid receptor VR1 innervation in the vestibular mucosa has been reported [16–19]. These nerves appear to be C-fibers and thus represent an increase in nociceptor density [16]. An increase in mast cells and subepithelial heparanase (a product degraded from mast cells) has also been described in localized vulvodynia, a possible trigger for stromal proliferation and intraepithelial extension of nerve fibers [20]. In addition, defective regulation of proinflammatory immune responses, with genetic variations in interleukin-1 receptor antagonist and melanocortin-1 receptor genes, resulting in more exaggerated inflammatory responses, has also been described in vulvodynia-affected women [21–25].

Local neuroinflammatory changes can activate silent nociceptors, upregulate sodium channels, and trigger genomic changes resulting in ectopic activity of nociceptors [10, 12, 25–28]. This has been referred to as the “ignition hypothesis.” A history of recurrent yeast infections is well reported among women with vulvodynia, supporting a possible inflammatory trigger, although this history should be interpreted with caution, as misdiagnosis of yeast is common. In one study, two-thirds of women referred to a tertiary clinic for management of chronic vulvovaginal candidiasis were found to have a noninfectious etiology of their symptoms, most commonly lichen simplex chronicus and vulvodynia [6, 29]. An altered immuno-inflammatory response to irritants and/or allergens and cutaneous hypersensitivity to *Candida albicans* is also described, supporting a triggering peripheral inflammatory event for some women [6, 30, 31].

Repetitive, painful, inflammatory triggers can affect both the central nervous system and the peripheral nociceptors. Repetitive depolarization of A-beta and C-fibers due to noxious stimuli displaces magnesium from its central binding site on the NMDA receptor. The NMDA receptor then becomes available to bind with the neurotransmitter glutamate, causing increased excitability of second-order neurons in the dorsal horn of the spinal cord [12, 21, 25–28]. This results in hyperalgesia, a biologically useful protective response to acute injury, where second-order neurons become more sensitive and depolarize in response to less nociceptive input [10, 14, 25–28]. However, repetitive noxious exposure can lead to changes in the CNS and sustained hyperalgesia long after the original injury or inflammatory insult has resolved. Therefore, a peripheral insult may be capable of inducing changes in the CNS that contribute to the chronicity of pain.

Vulvodynia is associated with an increased incidence of other pelvic pain syndromes [21, 32–34]. For example, the incidence of bladder pain syndrome/interstitial cystitis is 68–82% among women with vulvodynia as compared with a baseline rate among all women of 6–11% [12, 25–38]. The rate of irritable bowel syndrome is more than doubled: 27% among women with vulvodynia versus 12% in the general population [36, 39]. Another common comorbidity, hypertonic somatic dysfunction of the pelvic floor, is identified in 10–90% of women with chronic vulvar pain [12, 36, 39, 40].

Multiple genital pain syndromes may be explained by cross-systemic interactions between pelvic organs and somatic structures. The efferent and afferent neurons of the somatic and visceral structures in the pelvis converge centrally in the spinal cord at the S1–S5 levels [12, 41–44]. There are no second-order spinal neurons that specifically transmit visceral signals, so somatic and visceral efferents converge on the same second-order neurons in the dorsal horn [12, 44, 45]. While these interactions between pelvic structures are essential to coordinate appropriate function of the pelvic floor and urinary, gastrointestinal, and reproductive tracts, shared central segmental innervation allows neuroinflammatory changes to spread between organ systems [44–50]. In addition, animal models using a pseudo-rabies virus demonstrate that pathology can spread between pelvic organs, as neurogenic inflammation can produce end-organ inflammatory changes [12, 48, 51]. For example, experimentally induced inflammation of the colon or uterus produces inflammation not only in the intentionally targeted organ but also in the bladder and the skin [48].

The coexistence of multiple non-genital pain syndromes may also be explained for some women with vulvodynia by an underlying biologic vulnerability. Functional MRI in women with vulvar dysesthesia indicates altered central sensory processing similar to what is reported among patients with other pain syndromes, such as fibromyalgia, low back pain, neuropathic pain, and IBS [52, 53]. Further support for a systemic process or underlying biologic vulnerability is supported by the coexistence of chronic non-genital pain conditions in vulvodynia-affected women, such as fibromyalgia, migraine, and temporomandibular joint dysfunction (TMJ) [12, 36, 54].

Psychological and Emotional Contributors

Many studies have evaluated psychological and emotional contributions to chronic vulvar pain. Pain and depression are intimately involved—the incidence of depression among all persons with chronic pain ranges from 27% to 54% versus 5–17% for the general population [55–57]. The relationship is complex, as chronic illness in general is associated with depression; nevertheless, several studies have noted an increase in anxiety, stress, and depression among women with vulvodynia [58–60].

The neurobiochemical changes of depression, stress, anxiety, and pain are closely related. Depression, stress, and anxiety are all associated with changes in excitatory neurotransmitters, such as glutamate, substance P, and brain-derived neurotrophic factor (BDNF) [57, 61–64]. Substance P is algesic, glutamate is important in maintenance of hyperalgesia and upregulation of NMDA receptors, and BDNF is associated with abnormal neurogenesis and remodeling in the CNS [12, 25–28, 57, 61]. Prolonged dysregulation of the hypothalamic pituitary adrenal axis in response to the stress of chronic pain may also contribute [63].

The role of victimization in chronic vulvar pain is complex, with some studies noting an association between abuse and/or rape among vulvodynia-affected patients and other studies refuting that assertion [60, 65, 66]. Post-traumatic stress disorder, which can be the result of prior life trauma, is associated with changes in the cellular-mediated immune response systems (see Chap. 11) [65, 67]. Lack of family support as a child has been associated with an increased incidence of vulvodynia symptoms, and animal models confirm that exposure to early-life stress is associated with reduced synaptogenesis and expression of hippocampal glucocorticoid receptor mRNA levels and enhanced hypothalamic-pituitary-adrenal (HPA) responsiveness to stressors [63, 68].

Hormonal Involvement

Hormonal involvement in the genesis of vulvodynia has not been fully elucidated. Estrogen is known to affect inflammatory neuropeptides, and lack of estrogen is associated with increased density of sympathetic, parasympathetic, and sensory nerve fibers in the vagina [69–71]. Some studies support an association between oral contraceptive pills and vulvodynia, while others do not [72–75].

Diagnosis

Women who report vulvar pain, burning, or dyspareunia should be evaluated for vulvodynia. Given the increased coexistence of other pelvic pain syndromes, it is advisable to ask about the presence of pelvic pain, dysmenorrhea, painful bladder syndrome, and irritable bowel syndrome. Well-validated questionnaires exist for screening for interstitial cystitis syndrome (PUF—pelvic pain, urgency, and

frequency questionnaire) and IBS (ROME III) [72, 73]. Many women report irritation and exacerbation of pain with soaps, detergents, and sanitary napkins, so an inquiry into specific irritants is warranted, not only to identify potential triggers but to rule out the possibility of contact dermatitis as a cause for pain [36, 60]. Providers should ask specifically about the use of topical products that contain benzocaine, a local anesthetic associated with painful allergic contact dermatitis, and diphenhydramine, which is a common sensitizer [5].

Given the possible correlation with depression and anxiety, screening for these conditions is also recommended. There are many useful screening questionnaires such as the PHQ-9 for depression and the GAD-7 (generalized anxiety disorder-7) for anxiety. Inquiring about stress, coping, effect on intimate relationships, and history of sexual abuse or victimization is recommended [6, 7]. However, it is important not to further stigmatize women with chronic vulvar pain, many of whom have seen multiple providers or been erroneously told that their pain is “all in their head” because there is nothing visible on gross inspection to explain their symptoms. Screening all women with vulvar pain for these psychological and emotional confounders will help the examiner explain that these questions are not targeted towards specific patients but rather part of an attempt to identify all factors that may contribute to the individual pain experience.

Physical exam should begin with a careful evaluation of the external genitalia for lesions, erythema, and discharge to rule out contact dermatitis; nonneoplastic epithelial disorders, such as lichen sclerosus or lichen planus; and other skin conditions as a cause of the pain. After visual inspection, the vestibule should be evaluated with a Q-tip using light touch to identify areas of pain. The examiner should start externally on the vulva and move inwards towards the hymenal ring. Extreme pain with the gentle, light pressure of a cotton swab is allodynia. A diagram of the pain location and severity may be helpful [5]. The vestibule should be evaluated in the same fashion, typically tested at the 2, 4, 6, 8, and 10 o’clock positions [5]. It is important to note if the pain is confined to a specific region, such as the vestibule, or more generalized. If a pudendal nerve injury is suspected, the anal and bulbocavernosus reflexes should be evaluated and the perineum evaluated for areas of hyperesthesia or paresthesia that correspond to the distribution of the pudendal nerve [76].

A speculum exam should be performed, if tolerated, (the use of a pediatric speculum may drastically improve a patient’s ability to tolerate this component of the exam) to inspect the vaginal canal for lesions and discharge that could suggest an autoimmune dermatosis or an infections process. Discharge should be evaluated by office microscopy and a pH from the vaginal sidewall evaluated as part of the workup for yeast, bacterial vaginosis, and Trichomonas, all of which can cause dyspareunia. A vaginal culture for yeast (taken from sidewalls and posterior fornix) is also recommended as false negatives are possible with microscopy [5, 77].

After removing the speculum, an internal pelvic exam is indicated if tolerated. It is important to respect that many women with chronic vulvar pain have previously had negative experiences with pelvic exams and that not all women can tolerate an internal exam at the first visit due to apprehension, pain, or both. Talking about fears up front and proceeding slowly, informing the patient that she is in control and that the exam will be stopped if she is in too much discomfort, can be very helpful.

Starting with a single finger, the sidewall should be very gently palpated medial to the ischial spine to identify the pelvic floor muscles. The levator ani complex and obturator internus muscles should be palpated for pain, increased tone, and specific trigger points [76, 78, 79]. Very light palpation over the vaginal sidewall should be performed at the ischial spine over the approximate course of the pudendal nerve to elicit sharp, lancinating pain that might be suggestive of pudendal nerve injury [80]. Skin rolling over the perineum lateral to the anus is also believed to elicit pain in women with suspected pudendal nerve injury as a cause of vulvodynia. To make the diagnosis of pudendal neuralgia, corroborating findings, such as improvement of pain on standing, evidence of bladder and bowel dysfunction, and positive skin rolling, should be present. The examining finger should then be used to palpate the base of the bladder for pain, and finally, if tolerated, a full bimanual exam should be performed to rule out any uterine or adnexal pathology as a potential contributor to dyspareunia.

Treatment

Multiple therapies exist for vulvodynia and dyspareunia. The lack of level 1 evidence in this area only adds to the nuances and difficulties of management.

Local Skin Care Measures

The role of irritants in exacerbating vulvar pain symptoms is well described [5, 6, 60]. Irritants, such as perfumed products, soaps, and detergents, should be avoided. The vulva should be washed with water, although a mild pure glycerin soap or liquid castile soap can be considered for those women unable to go without soap or when there is menstrual blood that cannot be removed with water alone. The skin should be patted dry, and a hair dryer should not be used [5]. If sanitary napkins are irritating, switching to a chemical-free organic brand or even to all-cotton washable menstrual pads may be helpful for some women. Optimizing the barrier function of the epithelium by adding an emollient without preservative (such as plain petrolatum or vegetable oil) to the vulva skin after cleansing may help some women [5]. Removing pubic hair is not recommended as hair removal is associated with microtrauma to the skin, as well as removing a natural barrier to dirt and debris.

Diet

Restrictive diets, the most common being the low-oxalate diet, are widely reported in the lay press and by online sources. In one study of women with chronic vulvar pain, 41% reported trying a low-oxalate diet [81]. The idea stemmed from a single

case report in 1991 in which a woman with refractory vulvodynia was found to have periodic hyperoxaluria, and for this one patient, the addition of calcium citrate alleviated symptoms [82]. Dietary oxalate consumption appears to be the same among women with vulvodynia as compared with controls, and a prospective study of urinary oxalate levels in 130 women with vulvar pain and 23 controls found a similar distribution of oxalate levels between the two groups [83, 84]. Success rates on an antioxalate regimen range from 2.5% to 24%, which is equivalent to or worse than the placebo response rate in other vulvodynia studies [83–85].

Women with vulvodynia and either painful bladder syndrome or irritable bowel syndrome may find relief of their bladder or bowel symptoms with specific dietary measures aimed at eliminating bladder or gastrointestinal triggers [86, 87].

Topicals

Topical therapies are widely used for vulvar pain. Some women report improvement with application of plain petrolatum [5]. A prospective randomized controlled study using the topical Moisturel (petrolatum and dimethicone) as placebo identified a 33% response rate using four times a day application of this product. It is unknown if this response to application of placebo vehicle was related to the Hawthorne effect (attention and validation of pain and distress), a therapeutic benefit of the massage, improvement over time, or some other unknown factor [85]. Another study has also demonstrated a significant response rate to placebo topicals—a 46% improvement rate among women with localized vestibulodynia using acid mantle cream, a hydrophilic cream base, three times a day [88].

Topical analgesics are used frequently, either sporadic application during pain flares or regular daily application, to both provide analgesia and downregulate peripheral nociceptors [5, 90–91]. One method of application for localized vestibulodynia involves liberally coating a cotton ball with 5% lidocaine and then applying it to the vestibule overnight to optimize contact (at least 8 h). In this study, after 7 weeks, 76% were able to be sexually active compared with 36% prior to starting treatment [90]. However, a randomized placebo-controlled trial including lidocaine 5% cream in one treatment arm identified only a 20% reduction in pain for women with localized vestibulodynia, although this application process involved massaging the lidocaine into the vestibule four times daily versus the method of continuous nightly application. Interestingly, in this study, topical lidocaine was less effective than topical placebo which produced a 33% response rate [85]. Lidocaine gel has also been used, although some women report more local irritation with gel as compared with ointment [91]. Other topical anesthetics are described, but none have been studied [5].

Compounded adjuvant medications have also been evaluated. A retrospective study of topical gabapentin in PCCA Lipoderm base (PCCA, Houston, TX) in doses of 2%, 4%, and 6% applied three times daily for either generalized and localized vulvodynia indicates than 80% of patients had a reduction of at least 50% in pain score and 67% of women with localized vestibular pain resuming vaginal intercourse [92]. A retrospective review of 38 women using 2% amitriptyline/2%

baclofen in a Lipoderm cream for women affected with localized vestibular pain reported 53% of women experiencing at least a 60% improvement in symptoms but no change in frequency of sexual intercourse [93].

Two studies have evaluated daily applications of capsaicin in concentrations of 0.025% and 0.05% [5, 93, 94]. Some women with vulvodynia have been found to have increased vanilloid receptor (VR1) innervation, and capsaicin is a vanilloid receptor agonist that depletes substance P, affecting nociception [19]. However, the initial release of substance P causes significant burning on application, so pretreatment with local anesthetic to tolerate the capsaicin was recommended, which could potentially confound the results [94]. In one study, daily pain scores, as well as pain with intercourse, improved significantly for 59% of participants, but no patient had complete resolution of symptoms. In addition, within 2 weeks post-discontinuation of capsaicin, symptoms returned [93, 94].

While topical steroids are used by 34% of practitioners, and 22% use them first line, there is only one small prospective cohort study combining daily application of topical triamcinolone with oral amitriptyline indicating no advantage over amitriptyline alone [95, 96]. Topical estrogen is used by many providers, but there are no studies to support its efficacy [5]. Topical testosterone is not recommended, but there are no studies to support or refute this assertion [5]. Cromolyn cream 4% was ineffective in one study for vestibulitis [97].

Biofeedback

Biofeedback involves self-regulation of muscle tension and autonomic function. It is accomplished with surface EMG electrodes, either on the perineum or in the vagina. Normal resting tone of the pelvic floor via surface EMG (sEMG) measurement is <2 microVolts [78]. Many patients with vulvar pain have high-tone pelvic floor muscle dysfunction. Therefore, biofeedback can be used to reduce both muscle tightness and pain scores. Biofeedback, typically 20 min twice a day, improves pain scores for 35–93% of women with localized vestibulodynia and resumption of sexual activity for 69% of women [5, 91, 98–100]. A study looking at outcomes at 2½ years indicates success appears to be long term [101]. When intravaginal galvanic stimulation is combined with biofeedback, up to 79% of women resume sexual activity with up to 52% reporting pain-free intercourse at 6 months [98].

Physical Therapy

Addressing pelvic floor muscle hypertonicity can be helpful for many women with vulvodynia, and more than 80% of practitioners identify pelvic floor therapy as a very or somewhat effective therapy [102]. Treatment is typically performed by a physical therapist who performs an assessment of not only the pelvic floor but other potential contributing factors including, but not limited to, abdominal and psoas

muscles, sacroiliac joints, and the spine [78, 79, 103]. Treatment may include mucosal desensitization, internal and external massage, postisometric relaxation, ultrasound, and intravaginal galvanic stimulation (see Chap. 14) [78, 79, 103, 104]. Pain scores and pain during intercourse improve in up to 79% of women with localized vestibulodynia and 71% of women with generalized unprovoked vulvodynia [79, 98–101, 104–107]. Physical therapy has also been shown to reduce pain catastrophizing and pain-related anxiety in women with vulvodynia [105].

Adjuvant Medications

Adjuvant medications are non-analgesics used to treat chronic pain. The two main classes used for vulvodynia are antidepressants and anticonvulsants. More than 80% of practitioners feel that adjuvant medications are effective for vulvodynia [102]. It is important to understand that there is only one randomized, prospective study evaluating adjuvant medications for vulvodynia, and this study indicates a high placebo response rate: up to 33% with desipramine [85].

Success rates for tricyclic antidepressants and localized provoked vestibulodynia vary significantly. Randomized studies indicate that low-dose amitriptyline (10–20 mg) and desipramine 150 mg are ineffective for provoked vestibulodynia [85, 96]. Cohort and retrospective studies with higher doses of amitriptyline (40–60 mg a day) indicate more than 50% improvement in pain scores can be achieved for 47–59% of women with both localized provoked vestibulodynia and generalized unprovoked vulvodynia [108–111]. Gabapentin has been reported to produce more than an 80% improvement in pain scores for 64–82% of women with generalized unprovoked vulvodynia (retrospective reviews), and a small open-label prospective trial of lamotrigine indicates statistically significant improvement for women with generalized vulvodynia [112–114]. Pregabalin was reported to reduce symptoms by 80% for generalized unprovoked vulvodynia in one case report [115]. Nortriptyline, carbamazepine, venlafaxine, and topiramate are also proposed as adjuvant agents for vulvodynia [5]. Tricyclic antidepressants and anticonvulsants should be prescribed with caution for patients aged 65 years and older due to the increased risk of falls [117].

Injections

Local injections with a variety of agents for localized provoked vestibulodynia have been described including the following: steroids, botulinum toxins, and interferon. It is important to interpret these studies with caution as placebo response rates with injection therapy are significant [117].

Steroid injections are used for many chronic pain syndromes given their potent anti-inflammatory effect and the understanding that chronic pain involves a neuroinflammatory response [118]. A retrospective review of submucous injections of methylprednisolone and lidocaine indicates 68% of women had a complete or a

marked response and two case reports describe success with betamethasone [119–122].

Given their well-documented effect on muscle spasticity, botulinum toxins have been proposed as potential anti-nociceptive agents. A small case series and a case report indicated significant improvement with vestibular injections of 20–40 units of botulinum toxin. However, a randomized, placebo-controlled, double-blind study indicated no significant improvement for women with localized vestibular pain [118, 122, 123].

A deficiency in interferon-alpha production in women with localized provoked vestibulodynia has been described [124]. Weekly vestibular injections with interferon alpha provided substantial or partial improvement in 49–61% of women, although long-term improvement in these studies was variable and side effects were significant including fever, malaise, and myalgias [5, 125, 126].

Pudendal nerve blocks with triamcinolone are also described for women with generalized unprovoked vulvodynia due to suspected pudendal neuralgia. Ganglion impar blocks, steroid injection around the terminal branch of the sympathetic chain in the presacral space, have also been performed with good results for generalized vulvodynia [127–129].

Surgery

Vestibulectomy, resection of the vestibule and advancement of vaginal mucosa, is well described for women with localized vestibulodynia, and complication rates are low, with 3% of women reporting worse symptoms postprocedure and high satisfaction scores [130, 131]. Success rates range from 17% to 89%, although many studies are retrospective reviews and/or include nonhomogenous populations [85, 99, 101, 130–132]. A prospective study (level II) indicates a 52% reduction in pain scores for women at 6 months, and pain scores are not only maintained but continue to improve at evaluation at 2.5 years [99, 101]. Negative prognostic factors for vestibulectomy in some studies include primary vestibulodynia, higher pretreatment pain scores, low trust in treatment, and erotophobia [99, 101, 132].

Prospective studies indicate vestibulectomy yields a better improvement in pain scores than cognitive behavioral therapy, biofeedback, oral desipramine, and topical lidocaine [85, 99, 101]. However, it is important to note that even surgery carries a placebo response rate that is well described and vulvar biopsy alone has been associated with an improvement in pain scores in 67% of women [6, 16].

Complementary and Alternative Treatments

Use of complementary therapies is fairly common, with 31% reporting use of nutritional products, 27% herbal supplements, and 8% traditional Chinese medicine [133]. A small study of acupuncture for provoked vestibulodynia revealed significant improvement in provoked pain with manual genital stimulation but not coitus, and in a small group of women with generalized vulvodynia, 42% noted complete or significant improvement [134, 135]. Larger trials are needed to evaluate efficacy of acupuncture.

Management of Comorbid Conditions

Depression, stress, anxiety, catastrophizing, obsessive-compulsive disorder, and erotophobia are all negative prognostic factors with vulvodynia, so addressing these comorbid conditions is recommended [6, 32, 33, 36, 47]. In one study, three 1-h group sessions led by a gynecologist with expertise in treating provoked vestibulodynia resulted in significant improvement in psychological symptoms such as stress, depression and anxiety, and somatization, as well as improved sexual functioning [136]. Directly addressing psychosocial issues with cognitive behavior therapy improves both functional status and pain scores, although some women may need pharmacological management. Identifying and treating the secondary pelvic pathology such as the pelvic floor dysfunction or interstitial cystitis can also improve vulvar pain [6].

Summary

While vulvodynia is well described, many women go misdiagnosed for years. In one study, almost two-thirds of women saw at least three different providers before the correct diagnosis was made. Furthermore, designing appropriate treatment regimens is difficult given the paucity of well-designed, prospective studies. Further complicating matters is the high placebo response rate.

What is clear is that simply educating women about their condition and providing support is beneficial. Identifying and treating comorbid conditions, such as depression, anxiety, interstitial cystitis, and IBS, may also be of value. There is sufficient evidence to indicate that calcium oxalate diets are ineffective for vulvodynia, as is application of lidocaine four times a day and oral desipramine for localized vestibulodynia. There is evidence to support nightly application of lidocaine 5% ointment. Oral adjuvants, physical therapy, biofeedback, cognitive behavioral therapy, injection procedures, and surgery may all have a role for select patients.

Among women with provoked vestibulodynia, there is a growing body of evidence that vestibulectomy may be at least as effective if not more effective than topical and oral therapies, although screening for negative prognostic factors is definitely recommended. With the exception of all but a few studies, the lack of a placebo arm is a major confounding factor, given the high placebo response rate. Some authors have suggested a 50% or greater response rate for any therapy is required to reduce the possibility of placebo effect [85].

Overall, long-term outcomes are disappointing with up to 66% of patients report improvement and only 57% reporting greater than 50% improvement in pain since diagnosis [137]. Despite reports of "significant improvement," more than 50% of women still describe severe pain and some degree of functional impairment in activities of daily living. Some studies also indicate no change in frequency of sexual intercourse despite improvement in pain score—it is unknown if this is due to an underestimation in the degree of improvement or failure to control for negative prognostic factors such as depression and erotophobia [98, 137].

One study that combined two therapies, physical therapy and psychosexual therapy, achieved some of the highest success rates in improving pain scores and coital function, and so further investigation into integrated, multimodal therapy is strongly indicated [104].

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Chapter 7
Painful Bladder Syndrome/Interstitial Cystitis in Women

Leah Moynihan and Eman Elkadry

Painful Bladder Syndrome in Women

Introduction

Painful bladder syndrome affects thousands, if not millions, of women. However, the syndrome is not completely understood and is often incorrectly diagnosed. Despite ongoing research, there is a lack of effective treatments and understanding of the pathogenesis of chronic pelvic and bladder pain syndromes. This condition can occur in men as well, although symptoms are often blamed on chronic prostatitis.

The definition of painful bladder syndrome (PBS), also known as interstitial cystitis and bladder pain syndrome (BPS), has evolved over time. The term "interstitial cystitis" implies that there is inflammation within the bladder; this is true in only about one-third of patients with BPS.

Painful bladder syndrome is defined by the International Continence Society as "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology" [1].

The European Society of the Study of Bladder Pain Syndrome/Interstitial Cystitis uses the term "bladder pain syndrome," describing it as a "chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or urinary

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frequency" [2]. The Society of Urodynamics and Female Urology uses a similar definition, but symptoms must be present for at least 6 weeks [3].

The definition and terminology used to describe PBS will likely continue to evolve over time as there is better understanding of the pathophysiology.

Prevalence

It is difficult to estimate the prevalence of painful bladder syndrome given the variable definitions, populations, and survey methods used in the literature. In addition, PBS is often a disease of exclusion due to its poorly understood etiology [4]. Estimation of prevalence in the literature ranges from 10 to 865 cases per 100,000 people [5].

Etiology

The cause of PBS is not well understood. Theories have traditionally been split between two philosophies. The first focuses on the bladder as the main source of pathology and pain, and accordingly, treatment focuses on the bladder. In this theory, a bladder insult disrupts the protective layer of the bladder lining (called the glycosaminoglycan or GAG layer). The GAG layer protects the bladder epithelium from irritation by urine and bacteria. Potential bladder insults include a distension injury, bacterial bladder infection, or pelvic floor dysfunction. This allows solutes from the urine (such as potassium) to leak into the bladder lining, leading to tissue inflammation and epithelial injury. Tissue injury might also activate c-fibers (which carry nerve signals to the central nervous system). This, in turn, could:

- Lead to the release of substance P (which stimulates inflammation and aids in the transmission of pain)
- Activate mast cells leading to histamine release (which can trigger pain)
- Trigger an immune or allergic response

In this line of thought, treatment focuses on preventing or managing the factors that lead to tissue injury and pain.

The other school of thought centers around more generalized pelvic neurogenic inflammation, and thus, the bladder is secondarily affected along with other end organs. As pain in the bladder becomes chronic, there are changes in how painful stimuli are processed neurologically. This can lead to a lowered pain threshold and pain from non-painful stimuli (such as bladder filling).

This theory is consistent with the finding that women with PBS have a higher incidence of other painful conditions, such as irritable bowel syndrome and fibromyalgia. There also seems to be a higher incidence of PBS with other inflammatory and autoimmune complaints, as well as chronic fatigue syndrome [6, 7].

Regardless of the primary insult and resultant pain pathways, the pathophysiology does involve all the pelvic structures, including the pelvic floor [8].

Previous studies of women with IC have noted coexisting hypertonicity of the pelvic floor muscles [8]. These myofascial abnormalities, found on palpation of muscle and other tissue in the pelvis, are thought to contribute to the pain of PBS and irritative urinary symptoms [8–11]. However, it is unclear which is the primary cause and which is the effect. Release of pelvic floor muscles relieves urinary symptoms as well as pain symptoms.

An emerging body of research implicates systemic factors in the pathogenesis of urologic chronic pelvic pain syndromes, including abnormal hypothalamic-pituitary-adrenal axis activity and abnormalities in the sympathetic nervous system [12]. It is possible that IC/PBS represents the end organ damage of various inciting events that lead to local bladder inflammation, including peripheral and central neural upregulation, alterations in the hypothalamic-pituitary-adrenal axis, and changes in central perception and processing of nociceptive stimuli [12]. Similar pathways may also be responsible for vulvodynia and other non-urologic pelvic pain syndromes [13].

Several new lines of evidence also suggest a genetic component to disease pathogenesis. There is evidence to suggest that genetic risk factors contribute to chronic bladder and pelvic pain syndromes [14, 15]. Studies have shown familial clustering [14], and twin studies have also shown a possible genetic link [16]. This suggests that a genomic approach to diagnosis and treatment may be useful. In addition, at least one study has found that patients with PBS/IC have significantly more pelvic floor symptoms than controls, suggesting a possible propensity for this disease [17].

Symptoms

In clinical practice, women with PBS present with symptoms of bladder pain (especially with filling or emptying), bladder pressure, and dysuria, often with urgency and frequency (defined as voiding 8 or more times per 24 h). Some women also have dyspareunia, feelings of bloating or vaginal pressure, or constipation. Vulvodynia or other pain symptoms are often present as well. Women often have a history of being treated for recurrent UTI or recurrent vaginal infections, sometimes without testing or culture.

Symptoms often wax and wane over days to months. Patients can sometimes identify things that trigger or exacerbate their pain, including certain foods or drinks, sexual activity, physical activity, menses, or prolonged sitting. The foods and drinks most likely to flare symptoms include coffee, tea, alcohol, citrus fruits, artificial sweeteners, and hot peppers [18]. Stress is also often cited as an exacerbant [19].

Women with IC/PBS also have higher rates of depression, history of sexual abuse and symptoms of PTSD, anxiety, and perceived stress [16, 20]. Patients should be screened for these disorders during their workup.

Diagnosis

The diagnosis of painful bladder syndrome is based upon the presence of characteristic symptoms. A medical history and a physical exam are important both in confirming the diagnosis of PBS and ruling out other possible diagnoses, such as urinary tract cancer or stones, infection, overactive bladder, urinary retention, or a pelvic mass.

The history should focus on when symptoms began, whether there was an inciting event, if symptoms are chronic or intermittent, if there are factors that exacerbate or alleviate symptoms, and the symptom severity (using a 10-point pain scale).

A 24-h voiding diary can help to quantify how much and what type of beverages the woman is drinking and give an estimate of her bladder capacity. The diary should include the time and volume of each void and the time and volume for all fluid intake. This information can be used to educate the woman about bladder retraining and fluid titration and behavioral techniques that are useful in reducing frequency and urgency. If dietary triggers are suspected, a food and drink diary can help to narrow down the list of possible triggers.

Standardized questionnaires are used clinically and in research settings for diagnosing and monitoring painful bladder syndrome. Examples include the PUF (Pain, Urgency, and Frequency Symptom Scale) and the O'Leary-Sant Symptom and Problem Index. While these questionnaires might be useful for distinguishing painful bladder syndrome from other urinary complaints or monitoring symptom severity over time, experts agree that questionnaires should not be used alone to diagnose PBS [21].

The physical examination should include a complete gynecologic and urologic assessment of pelvic structures, including the health of external and vaginal tissues; assessment for vaginal discharge, pelvic masses, and urethral diverticula; as well as a rectal exam. In addition, a complete musculoskeletal assessment should be performed. Women with PBS often exhibit tenderness of abdominal, hip, low back, and thigh muscles. In addition, palpating the pelvic floor muscles, bladder base, and urethra during the bimanual exam usually elicits pain.

To examine the pelvic floor, place one or two fingers inside the vagina and apply pressure to the posterior and lateral vaginal walls while gently pulling towards the introitus. Normally, the woman should note a feeling of pressure during this examination. In women with PBS, there is often moderate to severe pain with palpation of the pelvic floor. This pain may refer to the bladder, urethra, rectum, or surrounding muscles. Laboratory tests should include a urinalysis and urine culture. Vaginal and cervical cultures are also performed as needed.

Cystoscopy and urine cytology should be performed if indicated, based upon physical findings and risk factors. Although cystoscopy is no longer required for diagnosis, it is important to eliminate other bladder pathology and sources of irritation; cystoscopy can usually be performed in the office.

In some women, it is not possible to complete an internal pelvic exam due to pain. In this case, it is reasonable to perform a pelvic ultrasound or examination under anesthesia (often with cystoscopy), especially if there is concern about underlying pathology.

There is interest in finding a urinary biomarker that could be useful in the diagnosis of painful bladder syndrome. Biomarkers are substances found in the

urine of women with painful bladder syndrome but not in normal women. One such biomarker is antiproliferative factor (APF), which was found to have a high sensitivity and specificity for identifying women with painful bladder syndrome. However, further study is needed to define the benefits, costs, and limits to testing [22].

Further diagnostic testing, including cystoscopy with hydrodistension, bladder biopsy, and potassium sensitivity testing, is not required to diagnose painful bladder syndrome. In addition, these tests can be painful and can delay the initiation of treatment. In the past, these tests were recommended to confirm the physical findings thought to be pathognomonic of painful bladder syndrome, such as bladder glomerulations, ulcers, and decreased bladder volume under anesthesia. However, studies reveal that healthy women with no symptoms of painful bladder symptom also have these findings [23]. In addition, these findings are not consistently present in women with painful bladder syndrome [24].

However, many physicians continue to recommend and perform these tests, particularly cystoscopy with hydrodistension. Some women get temporary relief of symptoms after this procedure. However, the relief is short-lived and only occurs in about 50% of women [25]. In addition, the procedure is usually performed under general anesthesia or sedation, increasing the cost and risks.

Treatment

Treatment for PBS aims to decrease pain and urinary symptoms. Evidence suggests that treatment should include a combination of pelvic floor physical therapy, medications, behavior changes, and psychosocial support. There is no single "best" treatment or combination of treatments for all women. In many cases, a woman will need to try several therapies to find the one(s) that works best. As the evidence for many of these therapies is lacking, treatment is often guided by physician preference and experience, anecdotal evidence, as well as patient preference.

Physical Therapy

Physical therapy (PT) for painful bladder syndrome is an important treatment to modify the dysfunctional pelvic floor musculature that contributes to bladder and pelvic pain [8, 26]. Pelvic floor physical therapy should be performed by a therapist who is experienced with myofascial and other manual release techniques. The therapy should aim to release tight, tender pelvic floor muscles, trigger points, scarring, and connective tissue restrictions and to desensitize hypersensitive areas (see Chap. 14). PT is best used in conjunction with other therapeutic modalities as many women with severe IC/PBS will need a combination of treatments. In our practice, PT is the most important of the interventions. PT can also be used as a primary treatment for women who do not wish to take medications or try more invasive approaches.

Pelvic floor physical therapy (PFPT) is usually done in 1-h sessions once or twice per week for at least 10 weeks. Depending upon the duration and severity of

symptoms, 1 year or more of weekly treatment may be required. The therapist works on the abdomen, hips, thighs, groin, lower back, and internal pelvic floor muscles (transvaginally, and occasionally transrectally). Treatment is done in a private room as the woman lies in the dorsal lithotomy position. Therapists will often supplement treatment sessions with home exercises and stretches. Patient acceptance is high [26] despite the perceived intrusive nature of PFPT and occasional pain flares with therapy. Logistical considerations such as insurance coverage, time commitment, geographic distance, and long wait times to begin therapy can impede treatment.

Behavior Modification

Many women with painful bladder syndrome empty their bladder frequently to avoid the pain associated with bladder filling. Making changes in voiding and drinking behaviors can help to relieve symptoms of urinary urgency and frequency.

Bladder retraining involves voiding at regular scheduled intervals during the day and slowly increasing the voiding interval over a period of weeks. The goal of bladder retraining is to restore a normal voiding interval (3–5 h) and decrease urgency. Initial voiding intervals are chosen based on a woman's current voiding frequency. As an example, a woman who currently voids every 30 to 45 minutes would be told to void every 45 minutes, by the clock, regardless of urge. She should use distraction techniques (crossing legs, counting backwards) if she feels the urge before 45 minutes. If she cannot wait, she may void sooner than 45 minutes. She would then restart the 45 minute interval. Intervals are slowly increased as the patient becomes more comfortable. Women who are able to follow this regimen often have an improvement in urgency and frequency [27].

An important adjunct to bladder retraining is fluid titration. This technique moderates the woman's fluid intake so that she drinks small amounts throughout the day rather than larger amounts at infrequent intervals. Although there is little data, we recommend that women drink 4–6 oz per hour throughout the day. This includes all fluids (e.g., milk on cereal, soup). If nocturia is a problem, we recommend that the woman stop drinking 3–4 h before bedtime. Obstacles to adherence include patients' work or activity schedule and the required motivation to follow this program. This type of regimen can be used as a general guideline for patients even if they cannot strictly adhere to the schedule.

Dietary Modification

There is widespread belief that particular foods, beverages, or supplements can trigger or exacerbate symptoms of painful bladder syndrome. Clinical studies are limited to retrospective, subjective reports [18]. Although the evidence is limited, we recommend that women avoid any item that they identify as a trigger. This might mean avoiding the item completely or avoiding it only during a symptom flare. We do not recommend eliminating entire food groups without guidance from a registered dietitian.

Activity Modification

Activity restrictions are recommended only if an activity is a trigger of pain or worsening symptoms. Although randomized trials are still lacking, exercise seems to improve chronic pain in patients [28, 29].

Medications

Oral medications used to treat painful bladder syndrome include pentosan polysulfate sodium (PPS), benzodiazepines, skeletal muscle relaxants, anticholinergics, chemical neuromodulators, and antidepressants. In our practice, we include medications when symptoms are severe enough to preclude waiting for the benefits of PFPT or behavioral changes to take effect. We always recommend medications in conjunction with both PFPT and behavioral changes.

Pentosan polysulfate sodium (PPS) is a drug that is believed to repair injured areas of the GAG layer. The standard dose is 100 mg 3 times per day on an empty stomach, although some providers recommend 200 mg twice per day. Treatment with PPS is recommended for 6 months before deciding if the drug is effective. If no improvement is seen at 6 months, it is reasonable to discontinue it. In clinical studies, PPS was more effective than placebo in relieving symptoms of pain, urgency, and frequency. However, the margin of benefit was small [30].

Since only a tiny amount of PPS reaches the bladder when it is taken by mouth [31], researchers have examined the benefit of giving PPS by the intravesical route, sometimes in combination with oral PPS. A combination of oral and intravesical PPS appears more effective than oral PPS alone [31]. Dosing for intravesical PPS is discussed below (see "Intravesical therapies").

Benzodiazepines, such as diazepam, clonazepam, and lorazepam, can be useful. While traditionally used for anxiety, the muscle relaxant properties of benzodiazepines can provide relief of pain related to muscle spasm. Similarly, *skeletal muscle relaxants*, such as cyclobenzaprine and baclofen, may have a limited role in the treatment of painful bladder syndrome. However, there are inadequate data to support long-term use of either benzodiazepines or skeletal muscle relaxants [32].

Treatment is started at a low dose once or twice per day. It is important to discuss the habit-forming nature of these medications with patients to ensure that they are willing to follow dosing instructions closely. In addition, patients should be told to use these medications only when bothersome symptoms are present, as in a flare, not as a preventive treatment. We reserve the use of these medications for severe cases to ease pain symptoms and to allow better sleep. Increased sleep has shown to help lessen PBS symptoms [33].

Anticholinergic medications are often given to address symptoms of urinary urgency, frequency, and nocturia. Examples include oxybutynin, solifenacin, trospium, darifenacin, tolterodine, and fesoterodine. These medications are similar in

efficacy but vary in cost, side effects, and dosing frequency. Side effects can be significant, with the most common including dry mouth, constipation, heartburn, blurred vision, and changes in cognition. There is no data on the effect of this class of medication on PBS/IC.

In women with painful bladder syndrome, anticholinergic medications are a reasonable option to consider, especially in women with urge urinary incontinence or disabling frequency. Behavior modifications are recommended in combination with anticholinergic treatment (see “Behavior modification” above).

Neuromodulating medications, such as gabapentin and pregabalin, are anticonvulsants that are also used to treat neuropathic pain. It is not clear how these medications work to relieve pain. There are limited studies of these treatments in women with painful bladder syndrome [34, 35]. However, anecdotal experience supports their use, especially in women with chronic, debilitating pain.

Gabapentin or pregabalin should be started at a low, once daily dose (usually at bedtime) and slowly titrated up to 3 times per day over 3–4 weeks, as tolerated. Side effects, such as drowsiness, dizziness, and difficulty thinking, can be limiting. Pregabalin can also cause peripheral edema and weight gain. If one drug is not effective, this does not preclude trying the other.

Antidepressants used to treat chronic pain include tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors. Amitriptyline is the most commonly prescribed tricyclic antidepressant for painful bladder syndrome. Clinical studies show that amitriptyline can provide modest pain relief, especially when taken at doses greater than 50 mg per day [36]. However, side effects such as drowsiness, dizziness, and other anticholinergic side effects can be limiting at this dose. Starting at the lowest possible dose and increasing slowly will help some women to accommodate to these side effects.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) were developed to treat depression but were found to relieve pain in some people with chronic pain. Two of the drugs in this category, duloxetine and milnacipran, are approved to treat pain; duloxetine is approved to treat diabetic peripheral neuropathic pain, chronic pain due to fibromyalgia and chronic musculoskeletal pain including that due to osteoarthritis and chronic low back pain, while milnacipran is approved for the treatment of fibromyalgia. SNRIs are a reasonable option for women with painful bladder syndrome who have chronic pain, especially women who cannot tolerate gabapentin or pregabalin. Side effects of SNRIs can include nausea and drowsiness. Starting with a low dose and increasing slowly can help to minimize side effects.

Antihistamines are widely prescribed for treatment of painful bladder syndrome, often in combination with pentosan polysulfate sodium (PPS). This is based upon anecdotal evidence that the activation of mast cells (as with seasonal allergies) can flare symptoms of painful bladder syndrome. The most commonly used antihistamine in women with PBS is hydroxyzine. However, clinical trials have failed to support its benefit [37], and we do not recommend it.

Several small studies have examined the benefit of cimetidine, an H2 antagonist [38, 39]. Although the studies found that cimetidine reduced symptoms, clinical experience has not supported its use.

In women with chronic pain, *opioid analgesics* are recommended on a limited basis due to their habit-forming nature and short-term benefit. In our practice, we refer patients who require opioids to pain management clinic.

Intravesical Treatments

Intravesical treatments for painful bladder syndrome are instilled by catheter directly into the bladder. The most commonly used treatment includes alkalinized lidocaine, sometimes in combination with heparin or pentosan polysulfate sodium (PPS). Clinical studies of lidocaine-based intravesical treatments reveal that they are effective in reducing pain and urgency, at least temporarily [40, 41]. The patient is instructed to hold the solution in the bladder for as long as possible (at least 30 min). In clinical practice, not all women benefit from intravesical treatments. In women who do benefit, pain and urgency can be reduced for hours to days. Patients who benefit can be taught to perform this treatment at home one to three times per week, with a return to the office if there are pain flares.

One combination of a lidocaine-based intravesical treatment includes 200 mg lidocaine, 40,000 units of heparin, and 8.4% of sodium bicarbonate (to reach a total volume of 15 mL). Pentosan polysulfate sodium (PPS) is sometimes substituted for heparin and is given at a dose of 200 mg (two 100 mg capsules) mixed with 30 mL buffered saline [31].

Intravesical heparin is given for its proposed benefit in strengthening the bladder surface mucin barrier. This is thought to decrease the sensitivity of the bladder to irritating substances in the urine. However, large-scale studies supporting the benefit of heparin are lacking. In addition, clinical experience reveals that it can take months to greater than 1 year of intravesical heparin treatment before improvement is noted [42].

Other intravesical treatments have been used to treat painful bladder syndrome, including resiniferatoxin, dimethyl sulfoxide (DMSO), bacillus Calmette-Guérin (BCG), and oxybutynin. However, clinical studies have not demonstrated consistent or effective pain relief with these treatments [43].

Botulinum Toxin A

Botulinum toxin (BTX-A) acts as a neurotoxin that inhibits the release of acetylcholine at the neuromuscular junction, therefore decreasing muscle contractility at the injection site. BTX-A is injected cystoscopically into the bladder at multiple sites. It is currently FDA approved for overactive bladder due to neurologic disease. Multiple studies have demonstrated it's efficacy in treating urgency, frequency, and urge incontinence even in patients without neurologic disease [44]. There has also been suggestion that BTX-A has anti-nociceptive effects on the afferent pathways in the bladder [45].

Adverse effects of BTX-A are usually temporary and include dysuria, hematuria, UTI, voiding difficulty, and need for intermittent self-catheterization (ISC). Patients must understand the risk of urinary retention and be willing to perform ISC. There have been reports of rare systemic reactions with BTX-A injections, including respiratory distress and even death, mostly in children with spasticity. Patients should be warned about these risks as well.

In a majority of studies of BTX-A, there were noted improvements in frequency, pain, voided volume, and quality of life indicators. Although there were varied methods, populations, and outcome measures, there does appear to be a trend towards benefit. Reported improvement lasted from 5 to 12 months in most patients [46]. Based on this potential improvement, patients with refractory PBS/IC may benefit from BTX-A injection.

Procedures

Percutaneous posterior tibial nerve stimulation (PTNS) is a procedure that involves placing a needle (typically an acupuncture needle) through the skin near the medial malleolus. The needle is connected to an electric stimulator to stimulate the posterior tibial nerve during a 30 min session that is repeated once weekly for 12 weeks.

PTNS was initially designed to treat overactive bladder and urinary urge incontinence. However, studies have yet to support the benefit of PTNS for women with painful bladder syndrome [47, 48].

Sacral neuromodulation is an FDA-approved treatment for symptoms of frequency, urgency, and urge incontinence. The treatment involves implanting a pacemaker-like device into the hip, which sends mild electrical impulses to the sacral nerves. The patient can control the device with a handheld programmer. It is thought to work by stimulating afferent nerve pathways (wyndaele.2000). There are a few reports of successful use of sacral neuromodulation for PBS/IC [49–52].

Potential adverse effects of sacral neuromodulation include pain, skin irritation, infection, device problems, and lead movement. The treatment is reversible, and the device can be removed. The battery must be replaced approximately every 5 years.

As with BTX-A, sacral neuromodulation is a reasonable option in women with severe, refractory symptoms. The use of test stimulation prior to permanent implantation allows patients to assess the potential benefit of treatment on a temporary, minimally invasive basis.

Surgical Procedures

Cystectomy and cystoplasty, with or without urinary diversion, are rarely performed now due to poor outcomes and high complication rates [53]. In addition, surgery does not always improve pain, likely due to neuropathic involvement and central pain sensitization.

Psychosocial Support

The value of psychosocial support for women with chronic pain should not be underestimated. Women with painful bladder syndrome often see multiple healthcare providers in an attempt to find the source of their symptoms. Because of the dearth of evidence supporting best practices in the treatment of PBS, many physicians are unsure how to identify and manage these women. This combination of factors leaves many women feeling frustrated, misunderstood, and unable to find relief from pain.

All women being evaluated for painful bladder syndrome should be screened for depression, either with informal questions or a validated questionnaire (such as the Beck's Depression Inventory II). Women should also be questioned about any past history of physical or sexual abuse. Several clinical studies have noted that women with PBS have a higher incidence of depression and past sexual or physical abuse [9, 54].

Psychosocial support is available from a number of resources, including local and online support groups, social workers, or psychotherapists. If anxiety or depression is suspected, the woman should be referred for further evaluation and treatment.

Complementary and Alternative Medicine (CAM) Treatment

There are a wide variety of complementary and alternative medicine (CAM) treatments advertised to treat painful bladder syndrome. As with some traditional treatments, evidence supporting the benefit of most CAM treatment is lacking. However, CAM appeals to many women with painful bladder syndrome due to its perception as being natural, safe, and under the woman's control.

Examples of CAM used for painful bladder syndrome include the following:

- Herbs and nutraceuticals, such as calcium glycerophosphate, L-arginine, mucopolysaccharides, bioflavonoids (such as quercetin), and Chinese herbs [20]
- Proprietary herbal blends including Algonot, Cystoprotek, and Cysta-Q [42]
- Guided imagery [55]
- Acupuncture [56]
- Exercise and yoga [57, 58]

Case-Based Discussion

AG is a 35-year-old G1P1 with 1-year history of frequency urgency, dysuria, and multiple treatments for urinary tract infection (UTI), but only one UTI was culture proven. She has also noticed vaginal discharge and has had numerous treatments for vulvovaginal candidiasis treated by her primary care physician and gynecologist.

She voids 15 times a day, 2–3 times at night. She notes hesitancy and pain with a full bladder. Intercourse is not painful but exacerbates her symptoms on the following day. Baseline pain is 3/10, but with pain flares, it is 8–9/10. She reports being anxious about her symptoms and often feels depressed. She denies a history of abuse. She reports no new medical problems or medications. Symptoms began suddenly without a clear precursor or trigger event except for the initial UTI. On further questioning, she does recall a fall off her bike about a year and a half ago.

She saw a urologist 4 months ago and was started on Elmiron (PPS) and low dose amitriptyline. Initially, these treatments seemed to help, but now she is not so sure. She does report some relatively pain-free days but cannot pinpoint a reason for good versus bad days. When symptoms are severe, she has been treated with ciprofloxacin, but cultures have always been negative. She had a pelvic ultrasound and cystoscopy that were reported negative.

On exam, she has normal weight, and her urinalysis is negative. There are no abnormalities on the abdominal exam except for tenderness over the rectus abdominis muscles. On pelvic exam, there are no lesions or masses. The bladder is not tender, but palpation produces an urge to void. Palpation of her pelvic muscles reveals high resting tone with inability to release. There is significant tenderness with palpation of the pelvic floor muscles, especially the obturators. Pelvic floor strength is fair at only 2/5.

Our treatment recommendations included referral to pelvic floor physical therapy, switch from amitriptyline to gabapentin, and behavioral changes (bladder retraining, fluid titration, relaxation techniques). We gave her information about local support groups and psychotherapists. To avoid making too many changes at once, we recommended that she continue Elmiron until she begins physical therapy. If her symptoms are improved at future visits, we can discuss discontinuing the Elmiron.

We plan to see her back in 8–10 weeks, after she has started physical therapy, to assess her status.

Patient Resources

There are a number of resources available for women with painful bladder syndrome. This includes online support and information, local support groups, clinical studies, and books.

Online support is available from the following websites:

- Interstitial Cystitis Network (www.ic-network.com)
- Interstitial Cystitis Association (www.ichelp.com)

Reliable sources of information are available from the following websites:

- National Institute of Diabetes and Digestive and Kidney Diseases (http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/)
- National Association for Continence (www.nafc.org)

For information about participating in a clinical trial:

- http://clinicaltrials.gov/

Books about painful bladder syndrome:

- *A Headache in the Pelvis: A New Understanding and Treatment for Prostatitis and Chronic Pelvic Pain Syndromes,* David Wise
- *The Interstitial Cystitis Survival Guide: Your Guide to the Latest Treatment Options and Coping Strategies* by Robert M. Moldwin

Conclusions

Painful bladder syndrome is a debilitating, potentially chronic condition that affects many women yet remains underdiagnosed. Research into the etiology and pathophysiology of PBS may help to better direct treatment approaches. A high index of suspicion should be maintained when seeing women with persistent frequency, urgency, or pain. A thorough history and physical is usually all that is needed. Additional testing will exclude underlying pathology. Triggers should be identified and treated as necessary.

Currently, physical therapy shows the greatest benefits but often needs to be combined with behavioral changes and medications. Treatment must be individualized based on the patient's symptoms and response to intervention and comfort level with treatment options. Newer modalities, such as Botox and sacral neuromodulation may be reserved for refractory patients that fail initial management approaches. Multidisciplinary care is often needed to address all patient symptoms and provide treatment of depression and develop coping skills.

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Chapter 8
Headache in Women

Carolyn Bernstein

Headache is one of the most common complaints in a primary care provider's office; the word is used to describe a variety of sensations, ranging from the deep throbbing pain of a migraine to the band-like pressure of a tension-type headache to the ache of trigeminal nerve irritation. Any pain on or around the head is often referred to by patients as "headache," and sorting out the etiology is a challenging prospect. In addition, there are gender differences with respect to headache, and consideration of the ecology of the patient is key. Headaches are divided into primary and secondary categories, with secondary headaches resulting from an external source, such as a tumor, infection, or vascular lesion, for example. The primary headaches are those for which there is no contributing factor.

Many headaches are identical with regard to diagnostic criteria and presentation in both men and women. It is essential when treating a female patient to recognize the potential varying presentations and factors that lead to the correct diagnosis.

For most types of headaches, men and women suffer in equal ratios, with the exceptions of two specific primary headaches: migraine and cluster. Cluster headache is not common and has a male to female ratio of 5:1. Migraine is far more common, affecting 33 million Americans, averaging 1 out of every 5 households, and with a female: male propensity of 3 to 1. It is not entirely clear why women develop migraine more frequently. Genetic transmission (genetic inheritance patterns have recently been clarified) and hormonal flux have both been suggested. Until the age of 12, boys tend to get more migraines; starting with puberty, the girls move ahead.

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Migraine itself surpasses even low back pain as the number one cause of missed days of work in this country and represents a huge financial impact on the work force. It is a common occurrence, yet often incorrectly diagnosed and undertreated. This chapter will help the provider to classify the type of headache from which female patients suffer, plan treatment including integrative therapies, and provide tools for follow-up. This chapter concludes with illustrative cases with management descriptions.

Diagnosis

Headache diagnosis requires familiarity with diagnostic criteria and excellent clinical skills. For most types of primary headache, there is no specific diagnostic test. The examiner needs to be familiar with varying presentations and to have a list of "red flags" with which he/she is familiar. Often, patients need to keep a headache diary in order to confirm the diagnosis.

The easiest way to think about headache is to divide primary from secondary headache as described above. Primary forms include migraine, tension-type headache, cluster, and some less common headaches. Secondary headaches result from another known cause, such as infection, tumor, vascular lesion, or trauma, and usually resolve or improve significantly once the underlying cause has been treated. The first question to ask is "When did the headache start?" Initial evaluation includes a thorough probe for causative factors, characteristics of the headache, location, duration, accompanying features, and previously tried treatments including medications and nonpharmacological therapies. Always during the initial evaluation, whether in the office, on the telephone, or in the emergency room, serious causes of headache should be considered. One must inquire if the headache is new and different, if there are any focal or lateralizing features, and about any signs of increased intracranial pressure such as worsening with bending over, nausea and vomiting, and increased severity in the morning. Positive responses should prompt brain imaging and further diagnostic workup; physical exam should include temperature and blood pressure recording, funduscopic exam, and careful neurologic examination.

Most headaches presenting to the office are benign in etiology. When seeing a new patient with chief complaint of headache, the evaluation process is identical, but the history may reveal that the headache has a chronic or periodic nature. One must be quite familiar with the diagnostic criteria for migraine with and without aura, as well as various types of tension-type headache. Idiopathic intracranial hypertension should be considered in young women who are overweight in particular; certain medications can raise the risk as well, including birth control pills, tetracyclines, and others. It is critical to evaluate properly as a missed diagnosis can lead to visual loss and even blindness.

Migraine is extremely common, with the nonaura type being most prevalent. There is often a family history; if not migraine per se, an older relative may have suffered from "sick headaches" or headaches that caused him or her to need to lie down in a

dark room. In order to make the diagnosis of migraine without aura, the woman must have had at least five episodes, lasting 4–72 h, with unilateral throbbing pain of moderate to severe intensity. The pain should get worse with movement and must be accompanied by either photophobia and phonophobia or nausea/vomiting. Secondary causes must be excluded. Migraines are frequently misdiagnosed as sinus headaches. Patients may present with pain and fullness in the face and behind the eyes, characteristics that are often consistent with migraine. In order to be a true "sinus headache," correctly titled "headache attributed to rhinosinusitis," there must be evidence – either clinical (e.g., purulent nasal discharge), imaging, or endoscopic – of an acute process, as chronic sinus inflammation has not been validated as a cause of headache. There may be an acute-on-chronic process present, but this must be validated as above.

Patients with migraine often experience both a postdrome and a prodrome; aura is a separate entity. The prodrome may include an anticipatory sense that the headache is about to occur. Some women will note food craving or frequent yawning prior to the onset of the migraine; others may have muscle tenderness or urinary frequency. Helping patients to recognize their prodrome is an important tool when planning treatment, as this will educate them to be aware that a migraine may be starting.

Aura is separate and probably occurs in 20% of patients or fewer. Visual aura is the most common variant, with a scotoma or scintillations, for example. This should be distinguished from blurred vision. Some women experience sensory aura, with numbness on one side or the other; some have word-finding difficulty and various types of aphasia. Data is emerging on more serious consequences of migraine with aura, such as increased risk of stroke, so it is critical to correctly distinguish this from prodrome. In order to make the diagnosis, women must only experience two migraines with aura, as opposed to the five necessary for migraine without aura.

Women are unique in experiencing hormonal migraine as well as menstrual migraine. The best way to ascertain if there is a hormonal component to a patient's migraines is to have her track her migraines in a journal and write down the dates of her period as well as any midcycle changes such as cramping that may coincide with ovulation. True menstrual migraine occurs on day one of bleeding ±2 days. Episodes must be consistently documented in this time period; a woman must keep a journal and track for a minimum of three cycles. Rarely is aura associated with menstrual migraine, although it may be present. This subset is separate from menstrually associated migraine, which occurs at least two out of three cycles, as well as at other times of the month.

Tension-type headache is equally as common in men as women. This type of headache is characterized by pain that is mild to moderate in intensity, often band-like in distribution, not throbbing, and not accompanied by other factors such as photophobia or nausea except to a mild degree. One must have at least ten episodes in order to make the diagnosis; headaches can be episodic or continuous and can become chronic if lasting for greater than 3 months.

It is worth mentioning sports-related headaches, especially in young women and girls. This is a growing area of concern and research. Postconcussive headaches include cognitive dysfunction as well as pain and can be acute or chronic. Girls and

women may sustain more head injury because their neck muscles may be less developed and thus less able to act as shock absorbers. There is also debate about whether girls are more scrupulous about reporting head injury; this is an ongoing area of research. When evaluating a posttraumatic headache, it is important to know if there was loss of consciousness, whether cognitive function has declined, and to consider neuroimaging.

With respect to other types of secondary headache, several may be unique in women. Headaches that present during pregnancy are always concerning. A unilateral headache, throbbing and pulsating with associated nausea, vomiting, photophobia, and phonophobia may be secondary to an arteriovenous malformation. While these vascular malformations are more likely to present with a seizure, generalized or focal onset, a new and different headache with these characteristics should provoke a careful evaluation. AVMs may be estrogen driven, and a small lesion may grow precipitously during pregnancy.

Another secondary headache that is often related to pregnancy is idiopathic intracranial hypertension (IIH), formerly called pseudotumor cerebri. Presentation is often similar to other headaches resulting from increased intracranial pressure: global throbbing pain, nausea and vomiting, worse in the morning or with bending over, and may diminish during the day. In addition, there may be focal neurologic signs on exam, such as papilledema, sixth nerve palsy or numbness, and weakness on part of the face or body. A question of IIH also merits an expeditious evaluation with imaging followed by lumbar puncture, careful pressure measurement, and immediate attempts to reduce the intracranial pressure.

Headache may also present as a sign of preeclampsia/eclampsia during pregnancy, and careful blood pressure evaluation as well as a urine screen for protein should be immediately performed. The headache must have at least one of the following three characteristics: bilateral, throbbing in nature, or worse with physical activity. Blood pressure must be greater than 140/90 for two readings at least 4 h apart; protein secretion is greater than 0.3 g per 24 h. The woman must either be pregnant or up to 4 weeks postpartum; the headache must develop during periods of elevated blood pressure and must resolve within 7 days of treatment. Other causes of both headache and increased blood pressure should be ruled out.

Etiology/Mechanism of Migraine, TTH, and IIH

Migraine has a complicated pathophysiology, now considered to be "neurovascular" in nature, combining more than one mechanism. Migraine represents a disorder of sensory processing, with multiple sensory expressions, for example, photophobia. Previously, migraine was considered to be primarily a vascular phenomenon, based on the throbbing nature of the pain, and the disorder and resulting symptomatology were believed to be secondary to vasospasm. However, pain is only one symptom, and our understanding of the pathogenesis of migraine has evolved tremendously.

Leao described cortical spreading depression as the explanation of aura at the onset of the migraine; electrophysiological and imaging studies have proven that CSD does exist and is linked to migraine by its activation of afferent nerves in the trigeminal meningeal region. CSD may explain both the aura and the pain of migraine. However, there is still no definitive proof that CSD acts as the trigger for migraine, and for many patients, the prodrome may begin prior to onset of the aura with changes in mood appetite and other factors.

In addition, migraine has an inflammatory component, as well as a component of brainstem dysfunction, although the precise location is not yet known. Studies continue using PET and electrophysiology to try to map the precise pathways.

Tension-type headache has multiple potential etiologies; the diagnosis is based on the duration and location of the pain as well as its characteristics. It may be muscular in origin, secondary to teeth clenching or neck spasm, or may be secondary to stress, dehydration, poor nutrition, or poor sleep, to name a few possibilities. In addition, hypersensitization of pain pathways, perhaps related to nitric oxide oversynthesis, resulting in abnormal pain processing may play a role in the development of tension-type headache.

As discussed above, idiopathic intracranial hypertension is an important headache to recognize due to its high morbidity if misdiagnosed. The pathophysiology has not been clearly delineated; the disorder may result from poor absorption or increased production of CSF. Distention may cause swelling along the optic sheaths as well as increased cerebral venous pressure.

Treatment

Treatment of headache is entirely contingent on making the correct diagnosis. Migraine in particular is often underdiagnosed, and before planning any therapy, medication or integrative, it is essential to understand the characteristics of the headache. Consultation should be sought for any questions or concerns; missing a "red flag" headache can have serious consequences, and treatment can be ineffective if the diagnosis is incorrect.

Pharmacologic treatment can be challenging. The first decision centers on whether a preventive plan is necessary for migraines that are frequent or severe or whether the headaches are infrequent enough requiring only an abortive treatment plan. Helpful tools may include the MIDAS (migraine assessment disability scale), which asks a woman to detail the number of days over the past 3 months that she has been either totally or partially disabled by her headaches. The results are grouped into categories from no disability to severe levels, and this often helps in treatment planning. For example, a woman who has just one or two migraines per month may be easily treated with an effective abortive plan; another woman may have upward of six migraines that are quite disabling and may prefer to use preventive therapies, both medication and integrative. The HIT (Headache Impact Test) is another quick form that can be filled out easily in the office and will help to plan appropriate therapy.

Preventive medications for migraine include the following classes: tricyclic antidepressants, anticonvulsants, calcium channel blockers, and beta blockers. None of these medications were designed specifically as a migraine preventive, and all have side effects to consider. The decision about which to choose should be based on the ecology of the patient: comorbidity, lifestyle, and characteristics of the migraine. Medications that decrease blood pressure (calcium channel blockers) and slow heart rate (beta blockers) may be poor choices for a woman who is athletic and participates in strenuous exercise. Topiramate, an effective anticonvulsant, may interact with certain contraceptives as well as cause cognitive dysfunction and weight loss. Valproic acid may cause hair loss and weight gain. Tricyclic antidepressants can be quite sedating and anticholinergic. In general, it is preferable to start with low doses of these medications and titrate to efficacy over a period of weeks. The woman needs to track both the frequency and severity of her migraines in order to objectively understand the efficacy of the treatment. It is also key to set appropriate expectations; patients often expect improvement within days and are disappointed when they learn that it may take several months to adjust the regimen. Some side effects, such as fatigue from a TCA or the tingling sensations that topiramate can cause, do decrease over time. Often, medications are most effective, both for compliance and therapy, when given in a once-daily formulation.

Menstrual migraine may be managed hormonally in some subsets of sufferers. There is data emerging about increased risk of stroke for those who have migraine with aura, and at this point, the recommendation is to avoid estrogen-containing contraceptives. Women who have migraine and smoke also have increased risk of stroke and should not be given estrogen. For those who have menstrual migraine without aura, using continuous birth control with just several withdrawal periods each year may afford significant relief. Before prescribing this therapy or adjusting hormonal treatments for fewer periods, the woman needs to carefully track her migraines for at least 3 months to be sure that she does meet the menstrual migraine diagnostic criteria. If so, and if hypercoagulable risk factors that would preclude use of estrogen-containing contraceptives have been ruled out (such as coagulopathy), continuous birth control may be an option. The intravaginal estrogen/progesterone ring is one preparation to consider; combination pills may be another.

There is some data that certain supplements may help prevent migraine. Evidence-based data exists for magnesium, riboflavin, and coenzyme Q10. One recent study demonstrated magnesium deficiency in 50 % of migraine sufferers; its use is often limited by tolerance, as it can cause diarrhea and gastrointestinal hypermobility. Riboflavin at the recommended dose of 400 mg per day is often part of a multivitamin preparation; CoQ10 can be expensive. These are worthwhile options for patients who cannot tolerate preventive medications or who would prefer to avoid traditional drugs.

Migraine abortives are a different category. Triptans are serotonin-receptor agonists that can abort a migraine effectively for many patients and come in different delivery modes. There are traditional tablets, melts, injections, nasal sprays, and new patches. Eight different types of triptans are available, each with a different time to action and duration of efficacy. It is important to think about the individual

migraine pattern when choosing which triptan to use. For example, a woman without aura, quickly crescendos with pain, and accompanying symptoms might do well with a very quick-acting zolmitriptan melt tablet, whereas someone who has a very slowly progressing but lengthy migraine may be a good candidate for a tablet that is absorbed more slowly but has a very long duration of action such as naratriptan. Combining the triptan with an NSAID at the anti-inflammatory dose will potentiate the triptan and also help to prevent rebound: for example, combining the triptan with 600 mg of ibuprofen may be far more effective than the triptan alone. There is one commercial preparation of sumatriptan and naproxen in one tablet. A woman's lack of response to a particular triptan should promote a trial of a different medication in this class as some people will respond to one type and not another. Dosing is also important: many patients require the maximum strength of the triptan for efficacy.

Risks of triptans mainly concern cardiovascular problems – if there is doubt as to whether a patient is safe to use these drugs, one can check the cardiac risk factor calculator.

There has been concern about serotonin syndrome resulting from interaction between triptans and SSRIs used to treat a comorbid depression. The American Headache Society has a review and evaluation of the data that led to the warning published in 2006. This reference notes that many patients benefit from the concomitant use of these medication types and that the risk of adverse consequences is minimal when triptans are used according to prescribing guidelines. The AHS website has a succinct evaluation of the topic that is patient-geared, and is an excellent tool for patient education. One concern about triptans, and all abortives, concerns medication overuse. It is critical to explain clearly how and when to take these medicines to help patients avoid overuse.

In order to be certain that the triptan medication is working, patients should record time until complete headache resolution and to note whether they need a second tablet. Patients should be informed that the medicine may cause tingling and palpitations as well as chest and neck superficial tightening sensations so that they are not alarmed.

NSAIDs are often excellent monotherapy as migraine abortives and are safe to use for many patients. It is important to use the anti-inflammatory, not analgesic dose. Often, dispensing prescription strength tablets requires fewer pills to be swallowed in the setting of an acute migraine and helps ensure compliance.

Older migraine abortives include various ergot preparations: tablets, nasal sprays, and suppositories. Ergots are sometimes combined in tablets with caffeine; the drugs can cause severe nausea and palpitations, and there are absolute limits on the quantities considered safe. They may be effective for patients who cannot tolerate triptans and are quite effective.

For many migraine sufferers, the nausea is as severe if not more so than the headache itself. These patients often need an antiemetic such as ondansetron or prochlorperazine. Metoclopramide is another option. Patients who suffer from vomiting will benefit from either suppositories or melt tabs; often, they are unable to use an abortive until the nausea is under control, so adding these medications to the

regimen can be very helpful. Patients often develop a secondary cervical stiffness or spasm, and a muscle relaxant such as cyclobenzaprine can also be tremendously helpful.

Rescue medications are those a woman may turn to if her abortive therapies have not helped. In general, narcotics are a poor choice, as they promote overuse and rebound headaches, and often transform head pain, causing it to become increasingly treatment resistant. For patients who can be extremely mindful, a small amount of acetaminophen with codeine may allow her to remain out of the emergency room and to get some sleep while the migraine dissipates. Patients may also benefit from taking a small amount of diphenhydramine and trying to sleep without introducing a painkiller.

Any type of ongoing migraine medication treatment regimen requires continual monitoring of the usage and efficacy of the drugs. If requests for abortive medication refills begin to accelerate, examine the women's diary and headache tracking to be sure she is not entering a medication-overuse situation. If this occurs, a careful detoxification scheme will break the cycle and help to get the migraines under control. Either a rapid steroid taper, during which abortive use is not permitted, or an injection of ketorolac may be of benefit. Through careful tracking and education, patients can become skillful at recognizing when their medication use is increasing.

Tension-type headaches may also require a preventive medication: tricyclic antidepressants are often a good choice, as are medications that can decrease muscle spasm such as baclofen. Usage depends on whether the headaches are episodic or chronic, and the frequency and disability the woman experiences. Triptans should be avoided as they are unlikely to afford relief for TTH sufferers due to their different pathophysiology. NSAIDs, however, can be an excellent abortive choice (brief mention of risks of NSAIDs). Also, consider shorter-acting muscle relaxants such as tizanidine or cyclobenzaprine used acutely for a TTH.

One abortive medication frequently used for a variety of primary headaches is a combination of acetaminophen, butalbital, and caffeine. Recent studies have demonstrated the lack of good evidence to support this choice and the potential for overuse and rebound. The combination is no longer available in Great Britain and should be used extremely cautiously. Patients may end up in such an overuse pattern that they are truly addicted to the barbiturate and require slow outpatient (and rarely inpatient) detoxification using longer-acting barbiturates such as phenobarbital.

Other specific treatments for secondary headache are available, for example, higher-dose steroids for the headache that results from an intracranial mass or hemorrhage, or acetazolamide for the increased intracranial pressure headache of IIH. These specifics will not be discussed here, and patients with complicated secondary headaches should be referred to a specialist.

Rehabilitation-based treatments are also an important consideration. Women with episodic headache often need a good abortive choice and a plan for what to do if the treatment fails. But for a number of women with chronic or daily headache, the disability is tremendous, and they often become homebound and unable to function. A number of headaches also have accompanying cervical strain and spasm, and musculoskeletal components, and this should be carefully evaluated with

consideration for a physical therapy or physiatry referral. Adding a small amount of exercise as tolerated may help to improve mood, although it will not necessarily help with the headaches. I thought there was some evidence that moderate daily exercise decreased frequency but not severity of migraine attacks. Many women report that any kind of impact activity, such as running or aerobics, can worsen migraine or provoke pain. Gentle walking and riding a stationary bike may be tolerable. Physical therapy can focus on the cervical spasm in order to increase mobility and flexibility and reduce pain.

Integrative therapies are another option either in addition to or in place of traditional treatments. There is not substantial research yet to demonstrate the efficacy of many of these alternatives, and insurers often will pay for very little if any of the treatments. Acupuncture is now widely available in this country. A 2009 review in the Cochrane Report did find evidence that traditional acupuncture might be more effective than preventive medications at preventing migraine. Acupuncture may also decrease the severity of an acute migraine attack, even if headache frequency is not improved. This treatment may be covered, even minimally, by some insurers and is a good treatment option for some women. Its use has not been well studied for other types of headaches.

Patients are often interested in herbal remedies. There are a variety of commercial preparations available in pharmacies that combine various doses of herbs with magnesium, for example. Butterbur, feverfew, and pedadolex are those most frequently used for migraine; concerns about precise dosing and potential interactions with other medications should be addressed. Patients may feel that herbs are more "natural" and need to understand the potential for side effects. In addition, efficacy data is only recently being assessed. As with any intervention, it is important to track outcomes.

There is tremendous myth and misunderstanding about nutrition and headache, mainly migraine. The Headache Council of New England has a statement paper on its website which states that there is no science to clearly support a "migraine diet" applicable to all. Individual food triggers may exist; a woman needs to track her diet and correlate with her headaches, as the headache needs to follow the food trigger within a 2-hour window. Stringent elimination diets are not evidence-based and are nutritionally unsound as well. Patients benefit from a review of healthy diet and nutrition, with instructions for keeping a food and headache diet to review in the office. Many adults are lactose intolerant, and this may be a trigger for some women, but dairy should not routinely be avoided until this has been clearly ascertained. The "migraine triggers" of cheese, chocolate, red wine, and nitrates may be important triggers for some individuals but do not need to be routinely avoided by all migraine sufferers. Dehydration may trigger a migraine, and women should be counseled as to adequate fluid intake. There is also debate about caffeine. No evidence to eliminate caffeine exists, although a caffeine headache is another important migraine trigger for some sufferers. Women may be able to have one or two cups of coffee per day, if they can adhere to the same amount at the same time.

Biobehavioral medicine has been studied, although not extensively, as a migraine treatment. Techniques such as biofeedback can decrease the anticipatory anxiety

around the headache as well as modulating the acute pain. Patients work with specialists to learn a series of breathing and relaxation techniques. Temperature regulation or other autonomic regulatory methods can be very effective and can be used by all, including those who cannot tolerate medications. However, certified specialists may not be available widely, limiting the usage. Often, insurance will cover this treatment under the umbrella of behavioral health.

There is little data to support yoga as a preventive treatment for headache sufferers, although there is tremendous interest in this practice. There are many types of yoga available, and patients are counseled to avoid the "power yoga" or "hot yoga," which can actually provoke headache. Restorative yoga, "gentle" yoga, anusura, and hatha yoga may be well tolerated and will, at a minimum, invoke relaxation. Much research remains to be done in this area.

A number of nonproven and expensive therapies exist and should be discouraged until further evidence is available.

Case-Based Discussion

Lily is a 22-year-old graduate student with no medical history other than migraines that began when she was 13. She gets one headache per month, so severe that it often causes her to miss school, and she must spend the day lying down in her bedroom. She has tried using ibuprofen when the pain starts without much relief. She is on no other medications. Her pain is unilateral and throbbing and comes on suddenly without warning, although she is beginning to notice food cravings for doughnuts and cookies prior to the headache. With the pain, she experiences tremendous nausea and vomiting and both photophobia and phonophobia.

When Lily started to track her headaches, she noticed that they were beginning consistently 1–2 days prior to her menstrual period. She had not realized this previously as she was not yet bleeding when the headache would start, and she had not realized that the food cravings were consistently associated with the headache. She charted an occasional mild headache at other times as well but not similar to the menstrual headache at all. Of note is that her mother had very similar headaches around her menstrual period, which were not present during pregnancy or after menopause. Lily does not get aura. She is a nonsmoker, has never had a blood clot, and has never been pregnant.

When considering how to treat Lily's headaches, it is key to make the correct diagnosis. She has menstrual migraine without aura, occurring within a 5-day window around day one of bleeding, and does not have concerning features for coagulopathy. After discussion, Lily started on a monophasic estrogen/progesterone-containing oral contraceptive and took a tablet consistently for 63 days before having a 7-day window of "withdrawal" bleeding. During that week, she was ready with a quick-acting triptan melt tablet to combine with 600 mg of ibuprofen; this effectively aborted her migraine three out of four times used. She was in a relationship with a male partner and had been using just condoms for contraception; she was

relieved to have the additional protection of the hormone-containing contraceptive pills. She has been stable on this regimen now for 2 years without incident.

Amanda is a 40-year-old laboratory worker with frequent headache that often begins with sparkles in her vision before the pain begins. When she charts her headaches, they are random, not associated with any food or other triggers, but often beginning later in the day. Her job involves leaning over microscopes and using the computer; she gets a half-hour lunch break but otherwise works consistently throughout the day. She notes a headache that begins with throbbing in both temples, sometimes one greater than the other, with marked photophobia and phonophobia. She may be nauseated but rarely vomits; her neck aches and feels tight, and wrapping an ice pack around her neck does help. She usually takes several acetaminophen/caffeine tablets and will do so at least 4 days per week. She rarely exercises and will leave work in time to pick up her children at their after-school program, rush home to prepare dinner, and is exhausted by the end of the day.

Amanda has both migraine with aura as well as cervicalgia and a component of trapezius spasm that is noted on her physical exam. Her job reinforces the stiffness and spasticity in her neck and shoulders; this is definitely associated with the migraine. She has a component of rebound headache as well from the frequent use of the OTC abortive; when this was noted, she became mindful of her usage of these medications. She preferred to minimize medications as much as possible. She was referred to a physiatrist for a course of trigger point injections in her neck and shoulders as well as physical therapy; her employer allowed her time once a week to attend sessions once the situation was explained. An ergonomic consult through human resources helped Amanda to obtain a better chair and work desk so that she was not continually leaning forward. She was given a triptan to combine with an anti-inflammatory for the true aura-preceded migraine and used ice consistently throughout the day. Her headaches, while not gone, decreased to four or fewer per month that she was able to successfully treat much of the time.

Women with headache have unique issues, both physiologically and socially, that must be addressed when evaluating and treating this complex medical problem. With the correct diagnosis and some creative ideas, there are a number of safe and effective treatments available.

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Chapter 9
Pregnancy and Postpartum-Related Pain

Colleen M. Fitzgerald

Introduction

The childbearing period is a time of remarkable reproductive and musculoskeletal change. Traditionally, women have been advised by both health care providers and other women that pain is a "normal" consequence of this life experience and a hardship that is simply a rite of passage into motherhood. The evidence, however, suggests otherwise. Pain in pregnancy for many women can be disabling and can lead to chronic symptoms if left untreated. The purpose of this chapter is to elucidate the prevalence, etiology, diagnostic strategies, and effective treatments for pain-related diagnoses in pregnancy and postpartum. Particular attention will be given to lumbopelvic pain, the most common pregnancy-related musculoskeletal complaint.

Types of Pain and Epidemiology

Low back and pelvic pain affects about 50% of pregnant women at some time during pregnancy [1]. Up to 76% of women can experience low back pain during pregnancy, and as many as 50% of these women take time off from work or have reduced social interactions due to their pain [2]. The persistence of such pain postpartum varies by study. In a 6-year follow-up study, most women experienced pain relief within 1–3 months of delivery [3]. A population survey study found that 68% of women with moderate to severe pain may continue to have pain after pregnancy [4]. Women with lumbopelvic pain during pregnancy also report higher levels of

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physical limitation after delivery and postpartum depression [5]. In fact, one in five women refrains from another pregnancy due to the fear of recurrent lumbopelvic pain [6]. Differences in reported prevalence and incidence rates of lumbopelvic pain during pregnancy are likely due to varying definitions of pain.

Pelvic girdle pain (PGP) is a specific form of low back pain. It may occur separately or in conjunction with low back pain [7]. Some studies include lumbar and pelvic pain as one group. Other studies consider PGP a distinct diagnosis. PGP is defined as pain experienced between the posterior iliac crest and the gluteal fold, particularly in the region of the sacroiliac joint. The pain may radiate to the posterior thigh and can also occur in conjunction with or separately in the symphysis pubis. Endurance capacity for standing, walking and sitting is diminished. In a Danish cohort study of 1,789 consecutive women at 33 weeks' gestational age, 24% of women had daily PGP diagnosed by history and an objective clinical examination [8]. PGP was classified into 4 distinct groups: double-sided sacroiliac (SI) syndrome (6.3%), pelvic girdle syndrome defined as daily pain in both SI joints and the pubic symphysis (6%), one-sided SI syndrome (5.5%), and symphysiolysis (2.3%), and a fifth miscellaneous group was defined as a daily report of PGP with inconsistent objective findings (1.6%).

Other types of pregnancy-related pain are reported but are not as common. They include cervical, thoracic, rib, hand, and wrist pain [2]. Carpal tunnel syndrome which is not always associated with painful paresthesias occurs in 7–43% of pregnant women when electrophysiologically diagnosed and can persist in more than 50% of patients after 1 year [9].

Risk Factors

A recent consensus study concluded that the single greatest risk factor for developing pelvic girdle pain during pregnancy is a history of low back pain [7]. Previous trauma to the pelvis can predispose a patient to PGP in pregnancy. History of oral contraceptive use, time interval since last pregnancy, height, weight, smoking, and age were not considered risk factors given the conflicting evidence [7]. The risk of developing pelvic girdle syndrome (pain in any of the three joints) increased with the number of previous deliveries in a large prospective cohort study of over 75,000 Norwegian women [10]. Diabetes also appeared to be associated with pelvic girdle syndrome [11]. A two times higher prevalence rate of sacral pain was reported in among IVF pregnant women in a small study [12]. Interestingly in a separate study, elite athletes were not protected against low back and pelvic girdle pain compared to controls [13]. Women with pelvic girdle syndrome during pregnancy had a markedly worse postpartum prognosis for long-term pain than those with single joint pain [8]. Additionally, it appears that women with PGP in the third trimester who have a higher sum of pain provocation tests on clinical examination and who have a history of pre-pregnancy low back pain are more likely to have persistent pain-related disability 12 weeks postpartum [14].

Potential Causative Factors in Pregnancy-Related Pain

The exact cause of pregnancy-related pain is unknown but is likely multifactorial. The etiology may be due to dynamic changes of the musculoskeletal structures (joint, ligament, muscle, bone), hormonal fluctuations leading to ligamentous laxity, and/or an inflammatory response to such alterations. Neurologic causes either peripheral (direct nerve injury) or central (sensitization) from other comorbidities may play a role. Changes in collagen composition [15] and bone mineral density [16] have been associated with persistent low back pain. Visceral causes of pain including urologic (renal stones), gynecologic (ovarian cyst), and gastrointestinal (appendicitis, cholelithiasis) sources must also be considered in this population (Fig. 9.1).

During pregnancy, a woman's body goes through tremendous changes that affect all organ systems, and the musculoskeletal system is no exception. Overall weight gain is on average 9–18 kg. A 20% weight gain may potentially double the force on a joint [17–20]. There is also a shift in the center of gravity, to a more upward and forward position [21, 22], as well as hyperlordosis, rotation of the pelvis on the femur, and an increase in the anterior flexion of the cervical spine and adduction of the shoulders [23]. The abdominal muscles stretch as the gravid uterus grows, while the muscles of the lower back work harder to maintain upright posture. The muscles of the pelvic floor bear the weight of the growing uterus and will eventually allow passage of the fetus. This creates a natural disruption of the "core" musculature. Inherent pelvic asymmetry associated with pregnancy may have effects on muscle

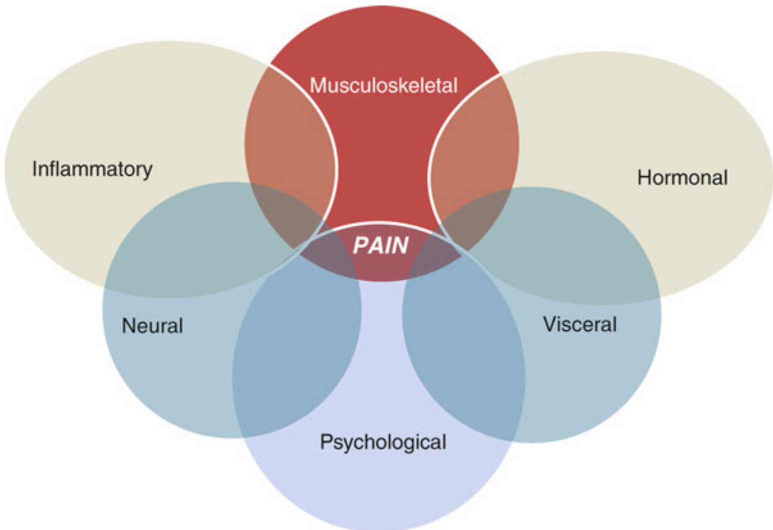

Fig. 9.1 Causal diagram of pregnancy-related pain

length that leads to suboptimal biomechanics. This may cause the pelvic floor muscles to have a less protective effect on the pelvic joints they surround.

The hormone relaxin has been identified as the major contributor to joint laxity during pregnancy [24]. There is inconsistent evidence showing that elevated serum relaxin levels correlate with pain [15, 25, 26]. Other studies show no correlation between relaxin levels and pain [27–29]. Relaxin levels increase during the first trimester, decline early in the second trimester to a level that remains stable throughout the pregnancy, and then decline sharply after delivery. Widening of the symphysis pubis and increased mobility of the sacroiliac synchondroses begin as early as the tenth and twelfth week of pregnancy as a result of relaxin [17]. The strong sacroiliac ligament which normally resists forward flexion of the sacral ala becomes lax due to the effects of relaxin [17]. Studies using an animal model have shown that relaxin has a potent effect on the amount of collagen in the nonpregnant rat pubic symphysis [30]. There is a clear relation between asymmetric laxity of the SI joints and pregnancy-related pelvic pain [31, 32], and such laxity increases the presence of postpartum pelvic pain by as much as threefold [32].

Clearly musculoskeletal changes persist postpartum, including pelvic floor muscle defects (pain and weakness), rectus abdominis diastasis, pelvic asymmetry or obliquity, and/or impaired load transfer with overall decreased core strength. Additionally, scar tissue (perineal or abdominal) may interfere with fascial support. Breastfeeding causes notable thoracic kyphosis and poor posture.

Differential Diagnosis of Lumbopelvic Pain

The sacroiliac joint (SIJ) is thought to be the most common source of pelvic girdle pain in pregnancy since most patients present with posterior pain [33]. Myofascial pain of the low back, pelvis, hip, or lower extremities can be seen in conjunction with other pelvic girdle diagnoses. Weakness and deconditioning of one muscle group can cause pain and dysfunction in another. Up to 52% of pregnant women with low back and pelvic pain have been found to have pelvic floor dysfunction [34]. Lumbar disc herniations are an unusual cause of low back pain in pregnancy, occurring in only 1:10,000 pregnant women [35]. True sciatica in pregnancy is actually rare [22] and is often mistaken for SIJ pain. Sacral stress fracture ought to be considered in patients with severe sacral pain both in pregnancy and postpartum [36].

Other sources of pain include coccydynia (fracture, dislocation, contusion) and hip pathology (degenerative joint disease, labral tear, transient osteoporosis of pregnancy) [37]. Pubic symphysis separation [38] is a rare but disabling cause of acute pain, most commonly seen postpartum, that is typically treated nonsurgically. Perineal pain is well documented in women with major genital trauma after vaginal delivery but usually resolves in patients with minor trauma at the 3-month mark [39]. Despite the high rates (20%) of levator ani injury postpartum in primiparous

women [40], no studies have linked such injury to persistent pelvic girdle pain postpartum.

Clinical History

The onset of low back pain or pelvic girdle pain is typically in the second trimester [41]. Patients may complain of low back pain, pelvic, buttock, tailbone, hip or groin pain of varying intensity and description. The pain often radiates from the low back into the buttock and posterior thigh past the knee and occasionally into the calf. Pain is typically worse with changing positions such as moving from sitting to standing or turning in bed. Walking with increasing speed and climbing stairs are other common aggravating factors. Patients may complain of pain at night or difficulty lying on their side. Some may describe numbness or tingling or give away weakness of the lower extremities. Pain is typically relieved at rest or in sitting. Many will describe the pain as disabling, causing limitations not just in mobility but also in job performance, childcare activities, and attempts at exercise.

Pregnant women commonly have urinary urgency and frequency as well as constipation as a normal course, and some experience the beginnings of stress urinary incontinence, particularly with coughing, laughing, or sneezing. Onset of sudden urinary retention, fecal incontinence, or numbness in the perineal area is of greater concern and should prompt the clinician to consider cauda equina syndrome. The patient's symptoms often make it difficult to differentiate between sacroiliac joint pain and a true radiculopathy related to lumbar pathology based on history alone. Physical examination can help differentiate these potential diagnoses.

Physical Examination

Appropriate physical examination of the pregnant patient is critical in making the correct pain-related diagnosis, especially since imaging diagnostics are limited. A detailed neurologic and lumbopelvic examination, including lumbar and hip range of motion testing, is the initial step. Abdominal examination particularly of the rectus abdominis musculature to assess for diastasis and an internal pelvic floor muscle examination to assess for pelvic floor myofascial pain or dysfunction may also be appropriate. A number of clinical tests for diagnosing pregnancy-related PGP have been investigated [7]; the tests with the highest sensitivity and specificity are discussed below. Most of these tests are designed to provoke a painful response in an affected pelvic joint region (sacroiliac and/or pubic symphysis), though they do not definitively discern the anatomic pain generator (bone, joint, ligament, tendon, muscle). The active straight leg raise test is considered a test of pelvic functional stability.

Patrick's Faber test: The patient is placed supine, with one leg flexed, abducted, and externally rotated so that the heel rests on the opposite kneecap. This test is positive with production of pain anywhere in the pelvic girdle.

Posterior pelvic pain provocation (PPPP) test (P4) [42, 43]: The patient is placed supine, the femur is flexed so that it is perpendicular to the table, and the knee is flexed at 90°. A gentle force is applied to the femur in the direction of the examination table. The test is positive when the patient experiences pain in the gluteal region of the ipsilateral leg.

Long dorsal sacroiliac ligament (LDL) palpation [27, 44]: The patient lies on her side with slight flexion in both hip and knee joints. The areas above both sacroiliac joints are palpated. Specifically, the LDL is palpated directly caudomedially from the posterior iliac spine to the lateral dorsal border of the sacrum. If palpation causes pain that persists 5 s after removal of the examiner's hand, it is recorded as pain. If the pain disappears within 5 s, it is recorded as tenderness. When the identical pain is felt directly in the vicinity but outside the borders of the ligament, the test is not deemed positive.

Pubic symphysis palpation [43, 45]: The examiner palpates the subject's pubic symphysis joint and checks for tenderness while the patient is lying supine. If palpation causes pain that persists 5 s after removal of the examiner's hand, it is recorded as pain. If the pain disappears within 5 s, it is recorded as tenderness.

Modified Trendelenburg's test [43, 46]: The standing woman turns her back to the examiner and, standing on one leg, flexes the other at 90° (hip and knee). The test is considered positive if pain is experienced in the symphysis.

Active straight leg raise (ASLR) test (for assessing lumbopelvic stability) [47, 48]: The test is performed with the patient supine with straight legs extended on the table with the feet 20 cm apart. The patient raises the each leg one at a time 30° above the table without bending the knee. The test is positive when the patient describes a heaviness or difficulty in performing the task. In the second part of the maneuver, posterior compression is applied at the iliac crests in a lateral to medial direction, and the patient is then asked to actively perform a straight leg raise. If there is greater ease in motion, this is considered a positive test.

Imaging

Imaging options in pregnancy may be limited due to potential radiation exposure to the fetus. However, most single diagnostic radiologic procedures are associated with little, if any, known fetal risks [49]. In deciding whether to perform an imaging procedure on a pregnant woman, the risk to the fetus must be weighed against the risk to the mother of making the wrong or delayed diagnosis by avoiding imaging. Ultrasonography and magnetic resonance imaging (MRI), which do not use ionizing

radiation, are the imaging modalities of choice during pregnancy [50]. There are no documented adverse effects of diagnostic ultrasound on the fetus, including duplex Doppler imaging, although there is concern that tissue temperature elevation (a function of the intensity, frequency, beam width, exposure time, and tissue composition) could have adverse effects [50–52].

There is no evidence for harmful effects to the fetus from MRI. Current data are derived from studies using 1.5 T or lower magnetic field strength [51]. Some individuals have raised concern about potential fetal harm resulting from the heating effects of radiofrequency pulses and the acoustic effects of noise [53]. The American College of Radiologists states that MRI may be used in pregnant women at any gestational age if the test is considered necessary by referring physicians [54]. Written informed consent is recommended. Animal studies of gadolinium show potential fetal toxic effects, although demonstration of fetal harm in humans is lacking (FDA category C drug) [51]. After maternal administration, gadolinium rapidly crosses the placenta and appears in the fetal bladder and then amniotic fluid, from where it is potentially swallowed by the fetus and absorbed through the gastrointestinal tract [55]. The fetal half-life is not known but is potentially prolonged. The American College of Radiologists recommends a “well documented and thoughtful risk-benefit analysis” before using gadolinium in pregnancy [54, 55]. Fortunately, gadolinium is not necessary for most low back or pelvic imaging [55].

Fetal exposure to ionizing radiation may result in (1) cell death and teratogenic effects, (2) carcinogenesis, and (3) mutations in germ cells. High-dose radiation exposure (much greater than that of a normal diagnostic procedure) before embryo implantation will likely result in embryo death. There is strong evidence that in utero radiation exposure increases the risk of childhood cancers, particularly leukemia, although the extent of the risk is controversial [51, 56]. The most common human teratogenic effects of ionizing radiation are growth restriction, mental retardation, and microcephaly [51]. The risk appears greatest for exposures between 8 and 15 weeks’ gestation. Data based on animal studies and epidemiologic studies of atomic bomb victims suggest that the risk to intelligence is linear based on dose, although the threshold for risk of severe mental retardation has been estimated at 60–310 mGy. Natural background radiation dose to the fetus during pregnancy is approximately 1 mGy. Computed tomography (CT) outside the pelvis/abdomen is associated with minimal fetal exposure and can safely be performed at any gestational age, provided the pelvis is shielded. The estimated mean fetal absorbed dose of an abdominal/pelvic CT is 30 mGy, although this can be reduced by altering parameters such as the slice thickness and pitch.

In the 2008 European guidelines for diagnosis and treatment of pelvic girdle pain, MRI was recommended for use in discriminating change in and around the SI joint and for excluding ankylosing spondylitis and traumatic injuries or tumor [7]. The guidelines state that there is no role for conventional radiography, CT, or scintigraphy (bone scan) in the diagnosis of pelvic girdle pain.

Treatment

Treatment options for low back and pelvic girdle pain during pregnancy include physical therapy, bracing, other treatment modalities (e.g., cold, transcutaneous electrical stimulation), acupuncture, and other complementary and alternative medical (CAM) treatments, oral medications, or intra-articular injection therapy. Surgery is reserved for patients with progressive neurologic disease such as cauda equina syndrome related to an acute herniated disc and is rarely necessary.

Physical Therapy

After activity modification, physical therapy may offer significant relief to patients with low back pain. A 2007 systematic review of treatment options for back and pelvic pain in pregnancy suggested that pregnancy-specific exercises, physiotherapy programs, acupuncture, and using special pillows result in better outcomes than usual care [57]. Adverse effects appeared minor or transient. However, the authors emphasized that most studies had moderate to high potential for bias, and further study is required. No studies address the prevention of back and pelvic pain. Physical therapy may also be of benefit postpartum. In a randomized controlled trial in postpartum women with pelvic girdle pain, women randomized to receive specific pelvic stabilizing exercises, in additional to routine physical therapy, had less disability 2 years after delivery than women who received physical therapy alone [58].

In general, studies show that women with low back pain who receive education and physical therapy report lower pain intensities and disability, higher quality of life, and improvement on physical tests. Physical therapy focuses on postural modifications, stretching, manual therapy, self-mobilization techniques, increasing awareness of symmetric body mechanics, functional rehabilitation, and core strengthening. Core strengthening involves strengthening of the muscles around the lumbar spine to maintain functional stability [59].

These "core" muscles include the diaphragm, transverses abdominis, multifidus, and gluteal and pelvic floor muscles. Transversus abdominis contraction decreases SI joint laxity to a greater degree than general abdominal exercise patterns [60] and strengthening the pelvic floor musculature has the capacity to increase the stiffness and stability of the pelvic ring [61]. Pelvic floor muscle training in pregnancy not only encompasses Kegel exercises but also includes endurance muscle training, relaxation and biofeedback, and functional retraining. In the postpartum period, pelvic floor muscle training can broaden to include electrical stimulation, weighted cones, and pressure biofeedback.

Complementary and Alternative Medicine (CAM)

In a multicenter Swedish study of 386 pregnant women with pelvic girdle pain, women randomized to receive stabilizing exercises in addition to standard therapy (education and home exercise) had less pain than women who only received standard therapy. The addition of acupuncture to standard therapy and stabilizing exercises resulted in even further reduction in pain [62]. A more recent study showed the benefit of acupuncture prescribed for 6 weeks for a total of 8 sessions in pain management at both gestational week 20 and week 26 [63]. Acupuncture is generally considered safe during pregnancy, although certain acupuncture points, which stimulate the cervix and uterus, should be avoided.

Other types of exercise, such as yoga, may be beneficial for overall physical and psychological distress in pregnant women as preliminary studies have shown [64]. A survey study on complementary and alternative medicine (CAM) therapies for low back pain in pregnancy revealed that pregnant women are not only open to such treatments but are recommended to pursue CAM therapies (massage, acupuncture, relaxation, yoga, and chiropractic care) by their primary care providers [65]. Although chiropractic care is commonly used for low back pain in pregnancy, the strength of the evidence for this is lacking [66]. One randomized control trial, however, compared osteopathic manipulative treatment (OMT) with usual obstetric care and obstetric care only for patients with low back pain in pregnancy. They found that OMT slows or halts the deterioration of back-specific functioning during the third trimester of pregnancy [67].

Modalities

Other modalities to treat back and pelvic pain have not been well studied in the setting of pregnancy. Deep heat is contraindicated in pregnancy (hyperthermia is teratogenic); therefore, cold modalities are preferred. Transcutaneous electrical nerve stimulation (TENS) has not been studied in pregnancy. Bracing in the form of a sacroiliac joint belt can be used for SI joint or pubic symphysis pain during pregnancy and postpartum though there appears to be insufficient evidence that wearing maternity support belts reduces pregnancy-related lumbopelvic pain [68]. The belt theoretically facilitates motor control of core stabilizing muscles and provides a sense of stability via joint approximation. Placement of the belt just caudal to the anterior superior iliac spines decreases SI joint laxity to a greater degree than if the belt is placed lower at the level of the pubic symphysis [69]. Studies have shown that the combination of a pelvic belt with muscle training improves pelvic stability and that the belt decreases the sagittal rotation in the sacroiliac joints by 19% [70].

Medical Therapy

Almost all drugs cross the placenta from the maternal to the fetal circulation. The medical management of pain during pregnancy is complicated by the need to limit the transfer of drugs across the placenta, particularly during the first trimester. Unfortunately, placental transfer of drugs and drug effects on the fetus are difficult to measure.

Drug teratogenicity is species specific and depends on timing of exposure, dose, and duration of exposure, maternal physiology, embryology, and genetics. The classic period of teratogenicity coincides with the period of organogenesis, between 31 and 71 days' gestation (starting the first day of the last menstrual period), although the central nervous system continuous to develop throughout gestation, and indeed during the first several years of life. Therefore, behavioral teratogenicity may occur secondary to drug exposure at any time during pregnancy.

The FDA uses a five-category pregnancy drug classification system (categories A, B, C, D, X); however, this classification has some major limitations. There are very few controlled studies in humans in which lack of fetal harm has been demonstrated. All new drugs are classified as category C (either animal studies have revealed adverse effects, but no controlled studies in women have been reported, or studies in women and animals are not available), and this does not help the practitioner or patient assess the drug's safety during pregnancy. Several Internet databases offer information on drug use during pregnancy and lactation, as well as a well-known reference book: Briggs GG, Freeman RK, Yaffee SJ, editors. Lippincott, Williams and Wilkins, Philadelphia (PA), 2008. Some drug companies maintain pregnancy registries for specific drugs.

There are no studies of drug use for the treatment of back and pelvic girdle pain during pregnancy. Acetaminophen is the first line analgesic drug of choice for the treatment of mild pain during pregnancy; however, it has no anti-inflammatory effect and has only mild analgesic properties. Low-dose aspirin is considered safe; however, higher doses should be avoided as they may be associated with an increased risk for placental abruption and other bleeding problems, and fetal gastroschisis [71]. Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause constriction of the ductus arteriosus and may have adverse effects on fetal renal function, leading to oligohydramnios. These drugs are not recommended for use for more than 2 days beyond the first trimester [71].

Opioids are not considered safe during early pregnancy and have been associated with an increased risk of birth defects [72]. Most literature regarding opiate abuse is derived from clinical experience with heroin and methadone; poor obstetric outcomes can be six times higher in patients abusing opiates [73]. There is a potential for neonatal abstinence syndrome after delivery in mothers exposed to opiates though this syndrome varies depending on type of opiate exposure [74]. The effects of maternal use of hydrocodone, which is more commonly clinically used in patients with acute low back pain, have not been investigated in any clinical trials.

Cyclobenzaprine, a muscle relaxant, is a class "B" drug. Data are inconsistent as to whether benzodiazepines are associated with increased risk of cleft lip and palate

and other congenital defects; however, in general, most practitioners try to avoid chronic benzodiazepine use during pregnancy. Diazepam is a class “D” drug. Lidocaine patches (class B) are presumably safe. Prednisone and prednisolone are inactivated by the placenta, and only a small amount crosses the placenta. Use in early pregnancy may be associated with an increased risk of orofacial clefts, and treatment of asthmatics with oral steroids during pregnancy is associated with an increased risk of preeclampsia and prematurity [75]. Use of corticosteroids in other medical conditions such as Crohn’s disease and asthma during pregnancy has not been associated with ill effect to the fetus [76, 77]. A low dose of tapering steroids has uncertain safety.

Breastfeeding mothers also have limited options for pain management postpartum. Acetaminophen, ibuprofen, prednisone, and short-term use of opioids are likely the safest for the infant; however, the evidence for such use remains scant [78–80]. Fortunately, good evidence exists for the use of specific exercise treatment for lumbopelvic pain postpartum and ought to be considered first line treatment in this group [81].

Interventional Procedures

Interventional injections have gained popularity in the treatment of low back and pelvic girdle pain. No studies have addressed their efficacy in pregnancy. Fluoroscopy-guided injections require exposure to ionizing radiation. Alternatives include blind injections, MRI-guided injections, and ultrasound-guided injections. Clinically guided blind SI joint injections are usually not successful; in one study only 22% of blind injections were placed intra-articularly [82]. Magnetic resonance-guided SI joint injection is safe and effective [83]. Ultrasound-guided caudal epidural injections had 100% accuracy in one study [84]. Ultrasound-guided SI joint injection may require more technical skill. In a study in nonpregnant patients, the percentage of successful injections increases with experience [85]. Local anesthetics appear to be safe for joint injection; the safety of glucocorticoid injection during pregnancy has not been established. For radicular pain, ultrasound-guided selective nerve root block is preferable to a caudal approach [86], and if ultrasound is not available, a blind interlaminar or caudal approach may be used. For axial back pain, ultrasound-guided caudal or interlaminar approach is recommended [87]. There is some data that suggests that blind corticosteroid injection to the ischiadic spine performed intravaginally has a positive effect on sacral pain in women with onset of pain during pregnancy [88]. During pregnancy, the skin should be cleansed with isopropyl alcohol or chlorhexidine as povidone-iodine (Betadine) has been associated with thyroid dysfunction in both the mother and the fetus [89].

Case Study

The patient is a 34-year-old female G2P2 currently 3 weeks postpartum who presents with left-sided low back and posterior pelvic pain immediately following vaginal delivery. She has no significant past medical history other than irregular menstruation during her college years. During this recent pregnancy at 28 weeks gestation, she had the onset of mild midline low back pain, 4/10 in severity, and underwent one physical therapy session. Her pregnancy was complicated by early cervical dilatation, and physical therapy was discontinued for weekly obstetrical evaluation. She delivered at 40 weeks gestation. During labor, epidural was placed but required additional dosing, and labor progressed rapidly. The patient pushed only three times in a dorsal lithotomy position, and she vaginally delivered a 10 lb 3 oz baby (4.63 kg).

Her pain is severe, left sided, and sharp in nature and is 10/10 at its worst. The pain is worse with weight-bearing, transitional movements, ambulation, stair climbing, and side-lying and supine positions and is better off-loading her left lower extremity. Ibuprofen provides minimal relief. She was seen by physical therapy for two sessions and then referred for further medical evaluation. She denies lower extremity numbness, tingling, weakness, or bowel and bladder changes. She is not currently breastfeeding.

On physical examination, she has an antalgic gait with decreased weight-bearing on the left lower extremity. Muscle stretch reflexes are 1+ in left Achilles and 2+ in right Achilles, 2+ in bilateral patella, medial hamstring, biceps, and triceps. Sensation intact to light touch and pinprick throughout and she has downgoing plantar responses bilaterally. Manual muscle strength is 5/5 in the right lower extremity, and 4/5 in the proximal left lower extremity due to pain and 5/5 in the distal left lower extremity. On musculoskeletal examination, she has a positive P4 test and Patrick's Faber test on the left, positive LDL tenderness on the left, tender left lower lumbar paraspinals, and a positive left active straight leg raise. Hip range of motion bilaterally is painless, but patient has pain with lumbar flexion. Differential diagnosis includes left sacroiliac joint dysfunction, left S1 radiculopathy due to disc herniation, external muscle strain/tear, sacral fracture, or pelvic hematoma. Plain radiographs of pelvis and lumbar spine show no evidence of fracture and mild disc space narrowing at L4–5 and L5–S1. MRI of pelvis reveals bilateral sacral ala fractures, mostly marked on left, and MRI of the LS spine shows L5–S1 disc bulge toward left approximating left S1 nerve root with mild left L5–S1 foraminal narrowing and degenerative disc disease with desiccation at L4–5 and L5–S1.

The patient was started on celecoxib 200 mg b.i.d., hydrocodone/acetaminophen 5/325 1–2 tablets every 6 h as needed, calcium 1,200 mg daily, and vitamin D 800 IU daily. She was restricted to relative rest for 2–3 weeks. An electromyography/nerve conduction study was ordered to rule out left S1 radiculopathy, and the study was normal. At 3-week recheck, exam was significantly improved. Physical therapy was ordered to focus on lumbar stabilization with extension bias, gentle pelvic stabilization, and core strengthening. The patient was referred to a PT specializing in women's health [www.womenshealthapta.org]. Repeat pelvic radiograph

at 11 weeks postpartum showed left pubic symphysis sclerosis and callous formation at the level of the sacrum.

Osteoporosis workup including bone density and endocrine panels (chemistry panel, 25-hydroxyvitamin D, TSH, PTH, beta-HCG, estradiol, FSH, serum and urine phosphate and calcium, parathyroid hormone antibody, alkaline phosphatase, osteocalcin, and urine collagen cross-linked N telopeptide) were normal except for slightly decreased urine calcium and decreased 1,25-dihydroxyvitamin D. After 8 weeks of physical therapy twice weekly, the patient was 90% improved and was able to return to full activity and initiate an exercise program. Although it is unknown, possible risk factors for sacral fracture in this case include rapid delivery, large-birth-weight infant, irregular menstrual history (relative estrogen deficiency), and mildly decreased calcium absorption with decreased 1,25-dihydroxyvitamin D and decreased urine calcium.

Conclusion

Pain in pregnancy and the postpartum period is common, particularly in the lumbopelvic region. Good evidence exists to support the use of specific clinical tests on physical examination, ultrasound or MRI for diagnosis if needed, and treatment focused mostly on education, exercise, and acupuncture. There are no pain medication trials in this population, and known data regarding the use of such drugs is derived from other medical literature. There may be a role for therapeutic injections in postpartum pain. Most importantly, greater attention should be paid to the diagnosis and treatment of pregnancy-related pain to avoid long-term disability and chronic symptoms.

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Chapter 10
The Female Athlete

Mimi Zumwalt

Definition/Introduction

Female athletes have unique concerns in terms of both anatomic and physiological issues regarding pain from musculoskeletal injuries and orthopedic conditions. Both mechanical loading and hormonal/endocrinological feedback strongly influence the female body structure. This chapter will examine gender-specific musculoskeletal disorders both in the acute traumatic and nonacute, atraumatic settings. Prevention and management of female athletic injuries will be addressed; the latter encompasses both surgical and nonoperative treatment.

Etiology/Mechanisms

Physical/Physiological

The fundamental differences between male and female anatomy stem from growth of lower extremity structure and alignment. This process begins during puberty and continues until skeletal maturity, which occurs during the late teens in females and up to 20 years old in males. In general, under the influence of estrogen and relative lack of testosterone, a young girl's pelvis widens in preparation for eventual child-bearing (see Figs. 10.1 and 10.2). As a result, the female lower extremity has an increased Q-angle as compared to males. The Q-angle is the angle formed by a line

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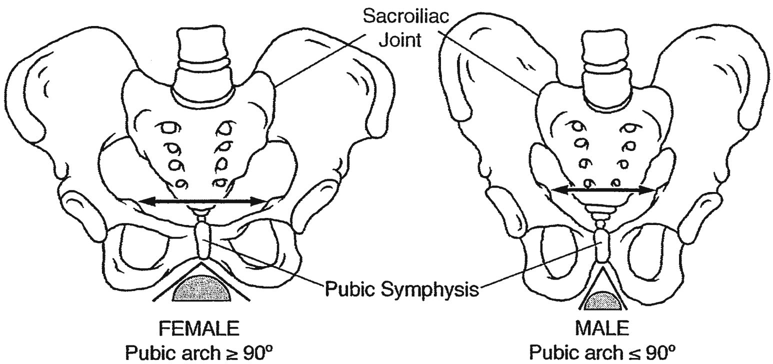

Fig. 10.1 Wider pelvic brim in females versus males

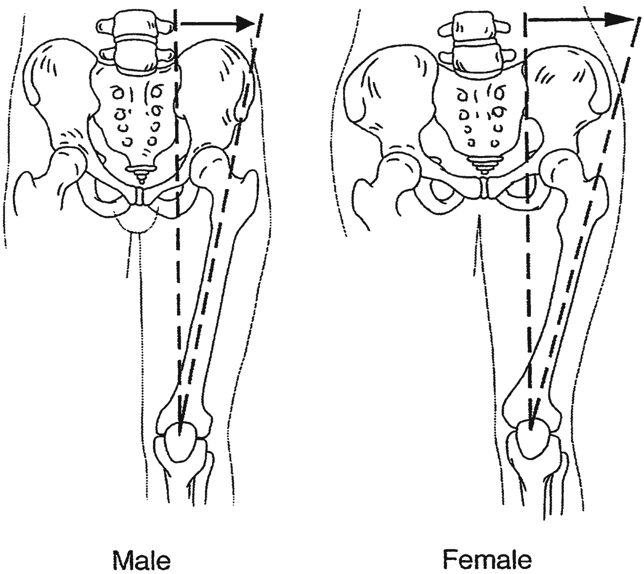

Fig. 10.2 Hip/knee angular difference

drawn from the ASIS to central patella and a second line drawn from central patella to tibial tubercle. An increased Q-angle is a risk factor for patellofemoral pain. In addition, in some females, the developing lower limb may take on a “crooked” shape spanning from the hips to the feet. This “miserable malalignment syndrome” (see Figs. 10.2 and 10.3) entails an increased Q-angle, genu valgum (knock knees), and pes planus (flat feet with midfoot pronation), all contributing to the lower extremity’s altered directional force, especially upon foot contact with the ground. The impact is therefore accentuated upon axial loading in the stance phase, especially upon single-leg landing from jumping activities, predisposing the knee to more

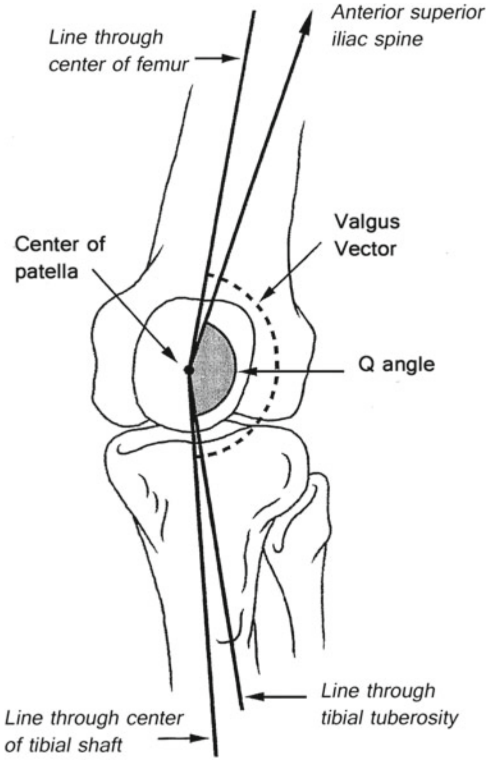

Fig. 10.3 Alignment/forces across the knee joint

injuries (see Fig. 10.4) [1, 2]. In terms of the upper extremity, females have less body length/shorter arm span and relatively less developed muscular strength as compared to males. As a result, they incur overuse injuries more frequently, especially with repetitive overhead activities/sports [3–5].

Specific Conditions

Upper extremity injuries to the shoulder (both micro- and macrotrauma) may result from water sports (diving/swimming), racquet sports (tennis/racquetball), overhead sports (volleyball/basketball), and throwing/pitching sports (softball) [1, 3–5]. Elbow and wrist injuries usually occur due to repetitive overuse and loading typical of sports with swinging motions and tumbling movement, respectively. Lower extremity trauma, from running and jumping sports, may include the hip, thigh, knee joint, ankle, and feet. Other, nonarticular conditions, affecting female athletes involve repetitive impact activities such as track and field events resulting in bone stress, which may eventually culminate in fracture [1, 6–9]. Finally, females with abnormal hormonal milieu from eating disorders and/or altered menstrual status,

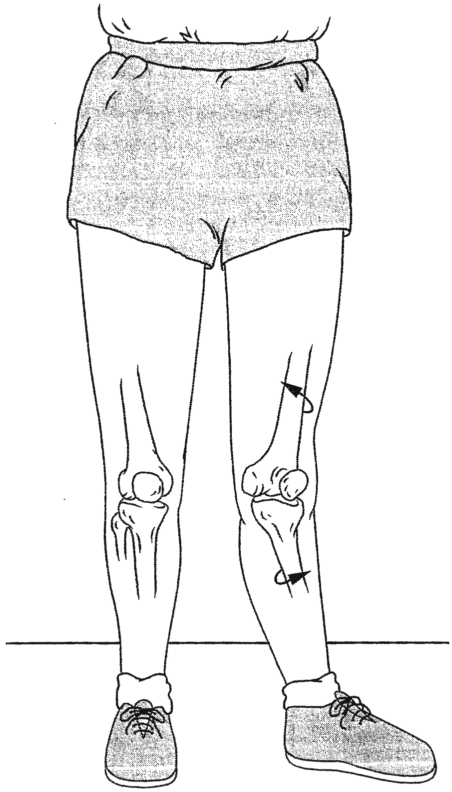

Fig. 10.4 Risky limb landing attitude

along with poor lifestyle choices such as excessive alcohol consumption or tobacco use are at increased risk for premature osteoporosis putting them at risk for insufficiency fracture. In some cases, the bone integrity of young female athletes in their 20s parallels that of a woman in her 70s [1, 7–9].

Shoulder Girdle

The shoulder girdle is made up of the ribcage, scapula, clavicle, humerus, glenoid, and their respective articulations.

Impingement syndrome (see Fig. 10.5) – This overuse condition occurs from repetitive overhead maneuvers, rubbing the humeral head on the underside of the acromion, causing friction, which results in edema and inflammation at the subacromial space, thus inducing pain and swelling with biceps tendonitis and/or subacromial bursitis. Eventually, this frictional wear may result in microtears of the rotator cuff tendons causing more pain and even arm weakness if there is progression of tendon damage [3, 10].

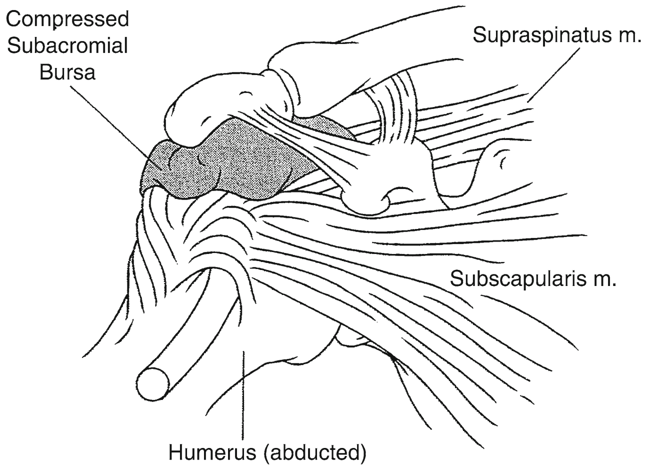

Fig. 10.5 Impingement syndrome

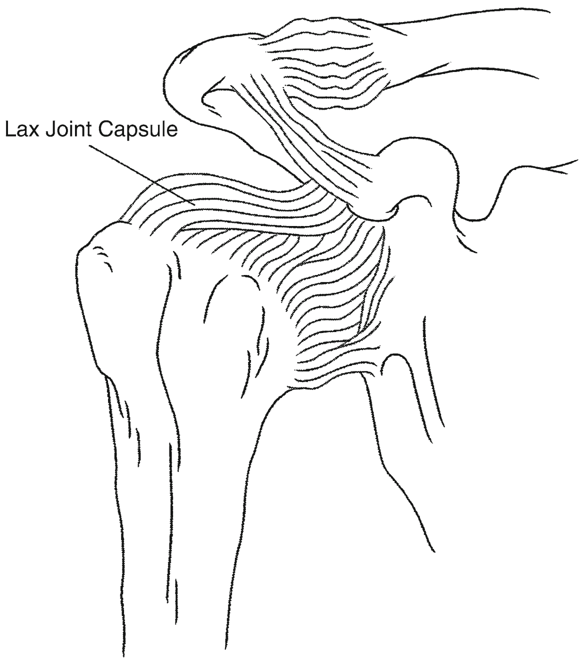

Fig. 10.6 Shoulder instability

Glenohumeral microinstability (see Fig. 10.6) – This occurs when there is laxity of the shoulder joint capsule causing the humeral head to sublux out of the glenoid, resulting in chondral wear and pain. The at-risk position is holding the shoulder extended/abducted/externally rotated, simulating the throwing position during

overhead usage. Systemic joint laxity (more common in females due to the hormonal milieu) along with weak rotator cuff/periscapular muscles both play a role in this shoulder condition [1, 3, 11].

Thoracic outlet syndrome (TOS) – This syndrome involves compression of a group of nerves and blood vessels descending through the axilla from the neck to the hand. Its frequency seems to be three times more common in women than in men. Possible etiologies include a long, aesthetic neck, weak surrounding shoulder girdle muscles, and/or extremely large breasts. Other potential causes are anomalous structures, i.e., cervical rib, fibrotic band formation from the clavicle to the spine, or abnormal clavicular anterior scalene attachment. Besides painful arm symptoms, other accompanying signs may manifest themselves as neurologic/vascular involvement (neurogenic pain and paresthesias) [3].

Elbow

Lateral epicondylitis or "tennis elbow," more appropriately termed tendinosis, is common in middle-aged women versus men – 10% as compared to 5%. This overuse condition is due to attritional wear/pulling of the extensor muscles' attachment from the arm bone secondary to repetitive forearm rotation maneuvers, especially with racquet sports. This condition occurs in golfers as well, although at lower rates [3, 5].

Wrist

Chronic wrist pain primarily occurs in competitive gymnasts due to repetitive axial loading of the upper extremity while performing tumbling stunts. In younger females with open growth plates, damage to the distal radial physis may result with potential growth arrest of the involved extremity. The risk is higher for those young athletes who start training later than 9 years of age as this adolescent growth spurt time frame makes them more vulnerable to injury [3].

Knee

Patellofemoral joint (PFJ) maltracking (see Figs. 10.3 and 10.7) causes anterior knee pain due to an angled force vector traveling from the hip to the knee to the ankle. The incidence of this common condition is 15–33% in adults and 20–45% in adolescents, with females being affected two to three times more frequently than males. This anatomical misalignment occurs more often in babies born breech and with firstborns. Pain is due to uneven wear of the patella off the trochlear groove

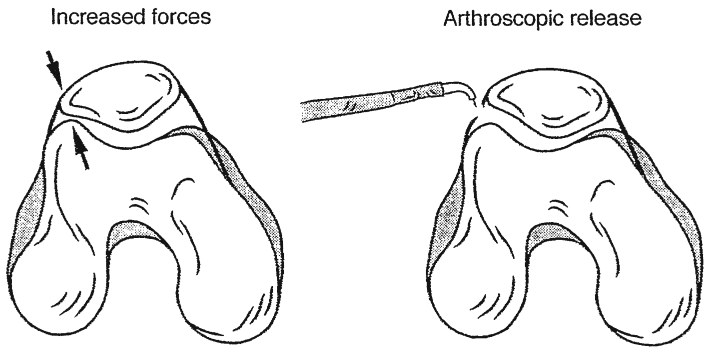

Fig. 10.7 Patellofemoral joint incongruency

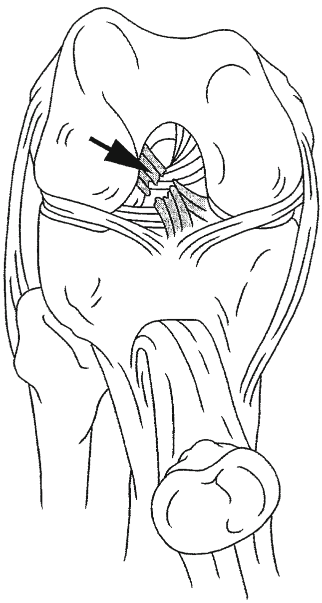

Fig. 10.8 Anterior cruciate ligament tear

causing chondral damage and/or patellar tendonitis. Volleyball players are more prone to this entity since they receive more stress repeatedly across the anterior aspect of the joint when diving for the ball onto their knees. Both cycling and running hills also tend to irritate the anterior aspect of the knee, most notably the PFJ, since the knee is continually flexed [1, 12–15].

Anterior cruciate ligament (ACL) tears (see Fig. 10.8) – Since the passage of Title IX of the Educational Amendment Act of 1972, requiring equality of females participating in any educational program that receives federal funding, the number

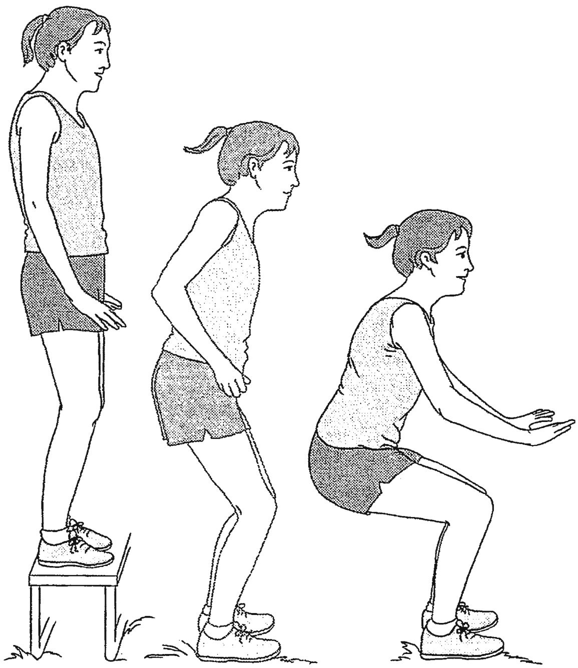

Fig. 10.9 Risky versus safe landing positions

of girls and women participating in scholastic sports has risen dramatically. With this rise in female sport participation, ACL injuries have occurred disproportionately much higher – up to 10 times greater in female than in male athletes. Possible contributing factors include increased joint laxity, femoral notch size/width, hormonal (estrogen/progesterone/prolactin) influence, shoe-surface friction/interaction, and perhaps most importantly, neuromuscular recruitment. Numerous studies have shown that, upon landing from a jump, postadolescent females are quadriceps (quad) dominant, activating their quadriceps muscle group prior to hamstring activation, thus placing an anterior shear force on the ACL. In contrast, preadolescent females, similar to males, are hamstring dominant, recruiting their hamstring muscle group before quad activation, a landing strategy that protects the ACL from tearing. The rate of ACL injuries in young female athletes peaks between 15 and 20 years of age, then decreases somewhat at the collegiate level, finally dropping to an incidence similar to males upon reaching elite status. The main sports most negatively accountable for ACL tears are primarily soccer, basketball, and handball. Approximately 75% of ACL injuries in female athletes are sustained from noncontact mechanism, especially upon single-leg landing in an at-risk position (see Figs. 10.4 and 10.9). Muscular fatigue from excessively prolonged training/competition may also play a role in this risk [1, 13, 14, 16–22].

Ankle Injuries

Grade I ankle sprain – Female athletes at the collegiate level have a 25% higher risk of mild ankle trauma as compared to males, especially basketball players. Risk factors have previously been alluded to, such as limb misalignment, lack of strength, and systemic joint laxity [23].

Achilles Tendonitis

Improper footwear, such as high heels, appear to play a role in this condition by shortening the Achilles tendon and lessening its flexibility, predisposing the tendon to microtears at the heel attachment.

Foot Problems

Bunion formation is also much more prevalent in females, exceeding males by nine times. Bursitis of the first metatarsal head prominence occurs especially in sports necessitating special footwear. Risk factors include a wide forefoot combined with a narrow shoe toe box, compounding the inflammation and causing pain from excessive pressure. Wearing high heels, again, especially in the case of flat arches may cause additional aggravation [1, 24].

Forefoot pain occurs primarily in sports requiring frequent starts and sudden stops, punctuated by decelerations (as in basketball). This maneuver makes the foot repetitively slide forward and backward inside the shoe, increasing frictional rub on the lesser toes causing inflammation and pain. This condition is exacerbated by wearing ill-fitting footwear. Again, female athletes are more susceptible due to having a wider forefoot and more narrowed hindfoot [24].

Stress Fractures

The incidence of stress fractures is 12 times more prevalent in the female than in the male. The tibia (see Fig. 10.10) is the most common place for stress fractures, comprising one-third to one-half of all stress injuries, followed by the metatarsals/foot, fibula, pelvis, and then femur. Other stress regions occur more commonly in certain sports, such as the ribcage in golfers and rowers and the pelvic/ischial rami in runners. These fatigue fractures present with groin or low back pain. Crossover running style and overstriding using the lower limbs both increase the risk of these overuse type injuries. These running techniques cause the hip adductors to pull on their origin – the pelvic rami – resulting in adductor/hamstring tendonitis and rami

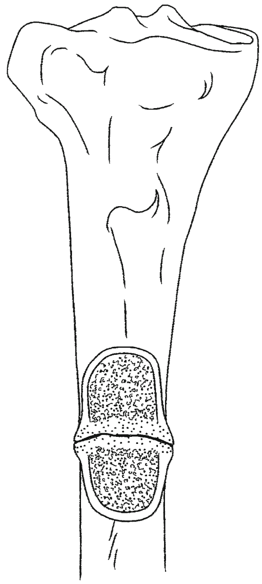

Fig. 10.10 Tibial stress fracture

stress fractures [1, 7–9, 25–31]. The “female athlete triad” (disordered eating, amenorrhea, and low bone mineral density) occurs most commonly in those females involved in aesthetic sports, i.e., dancing, gymnastics, bodybuilding, distance running, and figure skating. These athletic activities require competitors to be light and lean, thus pushing them to diet in order to lose weight to gain the competitive edge. Loss of bone mineral density can be devastating if not recognized early, as it increases the risk of osteoporotic fractures, bringing an athlete’s sporting career to an end. Therefore, all young female athletes should be screened aggressively for the presence of even the earliest signs of this disorder.

Diagnosis

Evaluation begins with a detailed history about chronology of symptoms, date of onset, timing, frequency, associated symptoms, aggravating and relieving factors, as well as quality, location, radiation, and severity of pain. Investigation also should delve into any change in training, footwear, equipment, or technique of athletic activities. A thorough physical exam is conducted, concentrating on the musculoskeletal, neurological, endocrine, and circulatory systems. Additional diagnostic studies include imaging to evaluate for acute injury in the case of trauma versus stress fractures in cases of more insidious onset. Plain X-rays are poor to evaluate for stress fracture, as findings will be normal during the subacute stage when many patients present with symptoms. MRI is the diagnostic test of choice to rule out stress injury, as it is both sensitive (even in early stages) and specific without the

added risk of radiation exposure. MRI is also helpful to help visualize any soft tissue involvement. Although bone scan is sensitive for stress injury, the test lacks specificity and is associated with radiation exposure. Lastly, electrodiagnostic and vascular studies can be ordered to rule out possible nerve compression or blood vessel involvement such as in the case of suspected thoracic outlet syndrome [32].

Treatment

Pharmacological – Medications should be used judiciously. Since analgesic properties of some drugs can have a symptom masking effect, athletes may be tempted to continue training and competing at levels beyond those recommended in the face of injury. The traditional mainstay of symptomatic treatment for musculoskeletal pain is NSAIDs (nonsteroidal anti-inflammatory drugs). The majority of these medications need to be taken with food to minimize GI upset. Metabolism is primarily renal, and, therefore, renal function should be monitored periodically during treatment. Nonanabolic steroids, such as cortisone, are potent anti-inflammatory medications with undesirable side effects, most notably immune system depression, and should, therefore, be thought of as a last resort for symptomatic management. Other modes of medicinal remedies include local modalities such as creams and ointments. Topical products containing menthol, such as Bengay and Biofreeze, are believed to relieve symptoms via a "counterirritant" effect based on the gate control theory. These types of treatments should be used sparingly since they may reduce pain without targeting the underlying problem. Instead, ointments such as sports cream (containing ibuprofen or other anti-inflammatories), which have deeper penetration to help with muscular inflammation/pain, are preferred. Systemic absorption has not been reported to be a huge problem with these superficial local modalities. Symptom masking may be an issue, however, in the case of more invasive methods such as deeper injections, usually a mixture of local anesthetic and cortisone are utilized (see procedural treatments).

Rehabilitation – Once a limb is injured, physical therapy exercises are vital to maintain strength in surrounding muscles and prevent disuse or inhibition atrophy. "Relative rest" such as engaging in cross-training (i.e., substitution of safer activities to maintain mobility while protecting the affected injured area) is important to avoid overall deconditioning. In the case of lower limb injury, activities, such as using an elliptical trainer, bike, or pool-based exercise, will lessen joint impact while maintaining cardiovascular endurance and to some extent lower limb strength. Supervised treadmill walking with a transition to jogging and finally running can be helpful during later stages of rehabilitation when the athlete is increasing activity in a gradual manner [1, 15].

Procedural – Injection of anti-inflammatory and pain-relieving substances is commonly used in athletic injury. However, steroid compounds, in particular, should be used judiciously as they may be associated with adverse effects. Steroid preparations should never be injected directly into tendons due to the high risk of tendon rupture.

In the shoulder, cortisone injections have the potential to aggravate an already torn rotator cuff. In the knee, intra-articular injections of cortisone may lead to chondrocyte death and eventual accelerated chondral wear, predisposing to or exacerbating degenerative arthritis. However, steroid injections are deemed fairly safe for the treatment of inflamed superficial bursae surrounding joints. Once injected, the beneficial pain-relieving results of these medications are variable both in quality and duration, ranging anywhere from a few days to a few months of lasting positive effects. The total number of steroid injections should not exceed three, separated by at least 6 weeks to allow healing between visits. With increasing frequency of administration comes increased risk of damaging surrounding intact soft tissue structures. Subsequent positive responses also tend to decrease with repeated injections in terms of length and degree of benefit [1].

There is an increasing interest among athletes and clinicians in a variety of injectable substances such as prolotherapy and platelet-rich plasma to heal sports injuries to ligaments and tendons, which are known to be poorly healing. Good quality research in this area is lacking at this time, and more evidence-based studies are needed before such treatments can be routinely recommended [1].

Surgical – Surgical management is only considered after the athlete has exhausted all conservative treatment, i.e., medications and physical therapy rehabilitation program. Traumatically torn structures are usually repaired and/or reconstructed (replaced with a substitute/graft). Overuse injuries are often amenable to arthroscopic and/or open debridement. Physical therapy should be strongly considered not only for full return to function postoperatively but also during the preoperative time period to hasten postsurgical recovery and prevent deconditioning.

CAM/integrative – Over the last several decades, there has been an increasing interest in the use of complementary and alternative medicine (CAM) modalities to treat various ailments. A 1993 survey found that 33% of adult Americans had used some sort of CAM in the previous year. In 1998, those numbers had increased to 42%. The most comprehensive information on CAM use was gathered by the National Center for Health Statistics (NHCS) as part of the National Health Interview Survey. In a recent survey of CAM use by intercollegiate athletes at a Division 1 NCAA university, 56% reported using CAM in the last 12 months with higher rates (67%) among female athletes. The most common forms of CAM used in this study included massage, chiropractic, and acupuncture.

Massage is the manipulation of body tissues using rhythmically applied strokes with varying amounts of pressure and stretching. The purported positive effects of massage include increased blood flow in muscles, increased lymph flow, a relaxing effect on the central nervous system, and loosening and prevention of adherent scar tissue. Massage has also been used to increase flexibility and coordination; increase pain threshold; decrease neuromuscular excitability; stimulate circulation, thus improving energy transport to the muscle; restore joint range of motion; and to relieve postexercise muscle soreness by removing lactic acid from tissues. The evidence regarding many of these purported effects of massage is lacking. However, massage has been utilized for its therapeutic effects in the context of athletics since early civilization. The use of sports massage has remained popular, despite the above mentioned lack of research.

Chiropractic is a drug-free, nonsurgical branch of health care that considers humans as integrated beings and gives special attention to structural, spinal, musculoskeletal, neurological, vascular, nutritional, emotional, and environmental relationships. The practice and procedures of chiropractic medicine are based on academic and clinical training received at accredited chiropractic colleges and include both diagnostic and therapeutic procedures. The mainstay of chiropractic treatments are adjustment and manipulation of various joints and associated soft tissues of the body, in particular that of the spinal column. In fact, although chiropractors may use various techniques including exercise and nutritional advice, the majority of the clinical and research literature involving chiropractic has focused on spinal manipulation.

Doctors of chiropractic are playing an increasingly active role in the treatment of athletes. They first officially participated in the care of athletes at the Olympic games in 1980. Chiropractic is now part of the sports medicine program of the US Olympic Committee. Due to the widespread use of chiropractic by athletes and the involvement of chiropractors in on-field sporting events, protocols have been published to guide chiropractors in treating the most common athletic injuries that occur in each sport.

Safety concerns still predominate among the medical community, especially when utilizing high velocity low amplitude (HVLA) manipulative techniques where there is an audible pop in the joint during the application of the chiropractic technique. Surveys have estimated that the incidence of vertebral artery dissection and stroke with cervical HVLA may be as low as 1 case in 5.8 million (based on malpractice claims) or up to 1 in 500,000 to 1 in 1 million (based on the report of neurologists). Data from Ontario, Canada provide estimates of serious adverse outcomes following cervical HVLA at 1.3 in 100,000. Estimates about the incidence of cauda equina syndrome following lumbar HVLA range from 1 case per 100 million to 1 in 1 million.

Acupuncture is part of a complex system of health care, known as traditional Chinese medicine that has been practiced throughout Asia for at least 2,000 years. Interest in acupuncture in this country has been growing since China's becoming more open to the U.S. in the 1970s. Today, acupuncture is practiced to a great extent in this country by both physician and nonphysician practitioners. An NIH consensus development panel that convened in 1997 found good evidence to support the use of acupuncture for postoperative and chemotherapy-related nausea and vomiting, nausea of pregnancy, and postoperative dental pain. The panel also found evidence to support the use of acupuncture as an adjuvant treatment for addiction, stroke rehabilitation, headache, dysmenorrhea, lateral epicondylitis, fibromyalgia, low back pain, carpal tunnel syndrome, and asthma.

The use of acupuncture by athletes to treat acute injuries is very common in Asia and Eastern Europe and is increasingly becoming an option in many Western nations. International exposure came at the Winter Olympics in Japan in 1998 when an acupuncturist in Nagano offered treatments to Olympic athletes. The public was stunned by the near miraculous recovery of the Austrian, Hermann Maier, in response to acupuncture. Maier took home the gold medal in the giant slalom and super G, 3 days following a dramatic fall that occurred during the downhill competition.

Maier attributed his quick recovery from shoulder and knee injuries sustained in that fall to his acupuncture treatments.

Over the last 30 years, a great deal of scientific evidence has accumulated to substantiate that acupuncture stimulation (AP) and electroacupuncture stimulation (EA) have physiological effects that strongly influence the pain modulatory, hypothalamic-pituitary, and inflammatory/immune systems. Although research regarding the majority of sports injuries are still lacking, particularly in the acute, traumatic setting, there is limited evidence to support the use of acupuncture in the treatment of knee pain, rotator cuff tendonitis, and lateral epicondylitis.

Acupuncture appears to be a safe and potentially effective method of treating pain and inflammation. There is sufficient evidence to suggest a physiological mechanism of action that involves neurohumoral processes that have both a central and peripheral effect. Clearly, better-designed and more specific studies are needed to assess the clinical efficacy of acupuncture in various sports injuries.

Case-Based Discussion

The athlete is a 22-year-old female who has been an avid soccer player since middle school. It is summer time and she is now playing for a local team in town that practices daily and plays three to five games a week within the league. She is also running on weekends to train for a half marathon scheduled in several months. Despite quadriceps and hamstring strains and intermittent patellar tendonitis, she has been able to withstand the rigors of daily impact activity. When experiencing pain or injury, she typically self-treats with over-the-counter analgesics (acetaminophen, ibuprofen, or naproxen), wears knee straps and/or braces purchased from a sporting goods store, and continues to participate in all activities.

Over the past couple of weeks, however, she developed increasing pain described as “achiness” in her leg after practices and games. This discomfort persisted despite her usual initial course of treatment and has begun to last longer after activity. Gradually, she began to experience symptoms during play, especially with longer duration of running and, finally, had pain even at rest.” She tried to play through the pain, which was partially masked by medications, until she collapsed after her leg gave out during a game while competing for a spot in a regional playoff.

Management

At this point the main goal should be to find the source of injury rather than purely proceeding with symptomatic management. In this case, after a history and physical exam was performed, the problem was localized to bony tenderness over the

anterior tibia. In light of negative radiographs for skeletal abnormalities, an MRI was performed revealing a tibial stress fracture. She was treated with conservative measures for 6–8 weeks with no impact activity and cross-training by using the bicycle and rowing machine for cardiorespiratory fitness. Weight training was also instituted to keep her muscles from further atrophy. Additionally, aquatic exercises were prescribed to lessen forces on her lower extremity. Her symptoms improved to the point where a jogging then running program was restored over the next 1–2 months. If pain has not subsided despite 3–4 months of conservative management, then use of a bone stimulator for fracture healing is an option. In rare cases, surgical intervention for stabilization of a non-healing fracture is necessary. Our patient was cleared for full sporting activity after the intensive physical therapy regimen was completed, several months after the bone was healed. She then underwent several more months of rehabilitation focusing on strength, endurance and agility training. Measures were then taken to hopefully prevent this overuse condition from happening again in the future!

In the acute setting, the basic protocol can be remembered with the acronym limb "**P.R.I.C.E**." First, *P*rotect the limb from further harm by instituting basic first aid treatment. Next, *R*est the limb. In the immediate postinjury setting, this may mean a period of limited weight bearing with an appropriate assistive device (most often crutches) with a gradual return to activity while healing occurs. ROM (range of motion) exercises should be performed during recuperation to keep joints limber and maintain muscle flexibility. *I*ce can then be used to reduce inflammation and pain. This is especially important during the first 24 to 48 hours following injury. *C*ompression of the injured area with a wrap further helps to reduce swelling, as does *E*levation of the limb (above heart level).

Use of NSAIDs should be especially limited during the first 72 h after injury so as not to blunt the physiologic inflammatory response that will be required for eventual healing of the affected area.

The clinical case above illustrates that too much training can have negative musculoskeletal effects since the body does not have time to rebuild and therefore is at risk for injury after repeated bouts of excessive loads. We, as health and fitness professionals, must monitor our athletes closely, watch for early warning signs, and intervene as soon as we can to help them slow down before drastic measures must be taken to treat their overuse injuries.

Patient Resources

American College of Sports Medicine
American Orthopaedic Society of Sports Medicine
American Academy of Orthopaedic Surgeons

Conclusions

Female athletes are a specialized group with nuances specific to their anatomical development. This in turn depends on hormonal and physiological influences, along with mechanical loading, to effect changes in their body composition/makeup. As a consequence, certain injuries occur more frequently in females, and it falls to us as physicians to recognize which type of trauma is most likely in these athletes. We want to prevent them from undergoing potential future traumatic episodes, thus enabling them to stay fit while playing their sport so they can be successful in winning game after game after game!

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Chapter 11
Immune Consequences of Early Life Stress: Relationship to Chronic Pain Syndromes

Linda L. Carpenter and Cyrena E. Gawuga

Introduction

Although a strong connection between chronic pain and mental health disorders has long been recognized by clinicians, by researchers, and even by many patients themselves, the specific nature of this relationship has been poorly understood. Clinicians' assumptions about the direction of causality between psychiatric syndromes and physical symptoms can greatly impact quality of patient evaluation and perhaps lead to suboptimal treatment of the patient presenting with pain. Patients' concerns about the clinician's assumptions with regard to these issues may lead to underreporting of important and relevant history or symptoms, which in turn may also promote suboptimal care. The common copresentation of chronic pain syndromes and mental health conditions may leave the clinician struggling with a *which came first?* mindset. Do mental illnesses cause the onset of physical pains or impair one's ability to cope with physical symptoms? Or, alternatively, does unrelenting physical discomfort lead to the onset of psychological symptoms and the development of psychiatric disorders such as major depression? A clinician's approach to the patient and choice of interventions may be dramatically altered when working with the understanding that a shared biological etiopathology can produce *either* a chronic pain syndrome *or* a psychiatric disorder or, perhaps more commonly, a presentation with features of *both* these conditions.

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While exciting advances in science have identified candidate genes and epigenetic changes that may determine risk for chronic medical disorders or psychopathology in adulthood, an equally impressive body of new research underscores the health consequences attributable to quality of early environment and the enduring impact of stress on developing neurological and other organ systems. Recent cross-disciplinary investigations have found associations between *exposure to stress during early life* and the emergence of a broad spectrum of pediatric and adult health outcomes [1], including migraine [2], irritable bowel syndrome [3, 4], fibromyalgia [5], interstitial cystitis [6], pelvic pain [7], osteoarthritis [8], rheumatoid arthritis [9, 10], psychological distress [11], substance use disorders [12], and other major psychiatric disorders [13–15].

Clinical data describing relationships between early life stress (ELS) and specific chronic pain syndromes (described in more detail below) are abundant and consistently underscore the relevance of quality of early environment when considering the adult patient. Though widely observed by clinicians and also described in the research literature for over a decade [16–18], significant advances in our understanding of the connections between childhood trauma, sensitivity to stress, and chronic pain syndromes have been more recent, as researchers have begun to elucidate a key role played by *the immune system* as a mediator for these relationships. Much remains to be discovered about how exposure to adverse environmental conditions early in the course of development leads to biological changes that manifest in one or more adverse health outcomes involving diverse organ systems (including gut, lung, brain, kidney, skin, peripheral nerves, musculoskeletal, and cardiovascular) decades later. Little work to date has revealed variables that confer resistance or protect certain individuals from developing symptoms and disorders in the wake of significant stress exposure. However, important insights have been gained about several risk factors. Numerous studies have reported abnormal stress hormone concentrations or aberrant stress reactivity among adult subjects exposed to ELS [19, 20]. In addition to enduring consequences of ELS on the neuroendocrine system, a growing body of literature now associates ELS with biomarkers signaling inflammation and immune system activation, even in the absence of infection, acute trauma, or other medical disorders [21, 22]. *The immune system thus appears to be a critical vehicle by which the consequences of ELS become manifest in patients with chronic pain syndromes.*

A clinician's understanding of immune system function and a general awareness of research findings pointing to immune regulation as a biological mechanism for stress-related disorders may be helpful in shaping attitudes, assumptions, and other aspects of evaluation and treatment of women with chronic pain. This chapter provides a basic overview of the human immune system, with concise descriptions of the "innate" and "adaptive" immune processes as they relate to chronic inflammation. Examples of animal models of stress exposure used to study the underlying biological mechanisms of pain are provided. We summarize converging evidence from preclinical and clinical investigations showing that immune system dysfunction is a consequence of stress exposure in a young organism and represents a common precursor to nociceptive pathology. Special emphasis is placed on findings relating ELS and immune function to the pathogenesis of two specific chronic pain syndromes common in women.

Overview of the Immune System

In essence, the immune system exists to defend an organism against external attack. Phylogenetically lower organisms, such as plants and insects, possess basic immune systems that protect them from bacteria, viruses, and fungi. In contrast, the vertebrate immune system has evolved into a complex assortment of response mechanisms that work together to protect against an astounding number of pathogens. The two major arms of the immune system, the innate system and the adaptive system, function synergistically. The innate system mounts the initial nonspecific defense against infection as well as alerts the adaptive immune system of the attack. In response, the adaptive immune system recruits effectors that create a robust and highly specific response to the invading microbe (or antigen).

Because foreign pathogens are always attempting to breach the body's defenses, the immune system is constantly "turned on." Although the immune system is highly tailored to rapidly respond to threatening external stimuli, the existence of autoimmune disorders and stress-related chronic inflammation indicates that the immune system's state of readiness sometimes leads it to attack the body itself, independent of the presence of pathogens. The overwhelming complexity of human immunology necessitates this overview focusing on describing only the basic components of the immune system, with a limited discussion of immune-mediated inflammation. More in-depth discussion of immunological concepts can be found in other highly regarded texts [23–25].

Innate Immune System

The innate immune system is the organism's first response to an external attack. Physiological barriers, such as the skin and mucous membranes, are capable of repelling most potential invaders. When the physical barriers are penetrated, molecular patterns on the invaders are recognized by pattern-recognition receptors, located on the surfaces of lymphocytes, or the "sentinel" cells of the innate immune response. These sentinel cells include macrophages, dendritic cells, and neutrophils.

Once the innate immune system identifies the invader, cells such as macrophages and neutrophils ingest, or "phagocytose," the foreign body and digest it. Phagocytic cells also produce cytokines and other mediators that further propagate immune activation; dendritic cells release cytokines and present antigen to cells of the adaptive immune system. Natural killer cells, a special class of lymphocytes, are activated by cytokines. Subsequent to activation, natural killer cells target and destroy cells that have been compromised by viral infection. The innate immune system is nonspecific and lacks "memory"; it responds to any given invader the same way every time. However, its rapid onset is crucial to the survival of the organism and to the activation of the adaptive system.

Adaptive Immune System

The adaptive immune system is brought "on line" by chemical mediators released during the innate immune response. Unlike the innate system, the adaptive immune system is highly specific, has memory, and is capable of recognizing an almost infinite number of antigens. There are two components of the adaptive system, humoral and cell-mediated. Effectors (such as cytokines) and antigen presentation both trigger activity of the lymphocytes of the adaptive system: T cells and B cells.

B cells, produced in the bone marrow, are part of the humoral arm; they produce specialized antibodies, which identify, neutralize, and eliminate antigens. The cell-mediated immune response is driven by T cells (generated in the thymus). Naïve T cells are presented with antigen by dendritic cells and macrophages, prompting the development of effector T cells. One of the effector types, helper T cells, produces cytokines that recruit cytotoxic T cells (as well as macrophages and B cells). Cytotoxic T cells destroy any cells with antigens that are inaccessible to antibodies, including macrophages that have phagocytosed antigens and are virally infected. After initial confrontation with an antigen, the adaptive immune system acquired immunological memory, which can last for years after the attack.

Inflammatory Response and Chronic Inflammation

Inflammation is the sequential response of the immune system in response to an antigen or other external attack. In the acute phase of inflammation, the immune system launches a three-pronged attack—hemodynamic changes (increased blood flow, vascular permeability), leukocyte recruitment and migration to the area of insult, and leukocyte release of circulating mediators (such as cytokines and C-reactive protein [CRP])—that determines more specific cellular pathways of the immune response [26].

Chronic inflammation occurs when the initial insult persists beyond a period of weeks to months. The primary goal of the chronic inflammatory process is to repair tissues affected by the acute inflammatory process. Lymphocytes, macrophages, and plasma cells are all recruited to the injured area of the body. Macrophages are key cells in chronic inflammation and are located in various tissues (e.g., central nervous system, liver, adipose), where they secrete dozens of inflammatory mediators [26, 27]. Of particular interest to stress and pain are the cytokines—tumor necrosis factor (TNF)-alpha, interleukin-1, and interleukin-6 (IL-1, IL-6). TNF-alpha is an "upstream" cytokine aiding in the initiation of the inflammatory response, while IL-1 and IL-6 are proinflammatory cytokines that propagate the inflammation process. IL-6, in particular, prompts the release of CRP from Kupffer cells in the liver. Interleukin-10 (IL-10), an anti-inflammatory cytokine, interacts with other systems, such as the hypothalamic-pituitary-adrenal (HPA) neuroendocrine system, to suppress inflammation and prevent hyperactivity of the immune system.

Neuroendocrine and Immune Responses to Stress: Clinical Research Findings

The hypothalamus, pituitary, and adrenal glands (comprising the HPA "axis") are the principal anatomical structures from which the effectors of the generalized stress response originate and are regulated. Corticotropin-releasing hormone (CRH) is the peptide that controls the anterior pituitary secretion of adrenocorticotropic hormone (ACTH), which in turn stimulates release of glucocorticoids (chiefly, cortisol in primates and corticosterone in rodents) from the adrenal glands. The brain discerns "stress" as a threatening or other noxious experience, interpreted within the context provided by physical features of the environment. In response to the stressor, the brain coordinates complex behavioral and physiologic actions such as succumbing, fighting, fleeing, and/or engagement in a variety of other behaviors that may ultimately promote or damage the overall health of the organism. The HPA-mediated neuroendocrine stress response interacts with the body's autonomic and immune systems, invoking an array of interregulating hormones, immune mediators, neurotransmitters, and other modulating elements that together act in allostatic processes to bring about adaptation to stressors.

Once thought to be pathognomonic of major depression, abnormalities of HPA function have now been demonstrated in adults reporting childhood maltreatment or other types of ELS such as preterm birth or socioeconomic adversity, independent of mental health disorders [28, 29]. Both exaggerated [30] and diminished [31] patterns of cortisol release have been described, with similar patterns of relative abnormality observed in psychiatric patients as well as in nonpsychiatric community samples exposed to ELS [28]. Neuroendocrine findings such as relative hypercortisolemia have also emerged in studies of chronic pain patients [32, 33], though the relationships between HPA axis effectors and pain are highly complex, with apparent paradoxical effects related to dose and location in the body [34, 35]. Non-adrenal sources of glucocorticoids and tissue-specific modulation of glucocorticoid exposure [36–39] may be factors contributing to seemingly discrepant or paradoxical findings.

Stress and HPA axis hormones have shown both enhancing and suppressive effects on immune system activity as a function of dose, duration, and timing of exposure [40]. Communication between glucocorticoids and cytokine immune mediators is thought to be bidirectional [41], but the mechanisms by which chronic cytokine exposure impacts HPA axis function and promotes many physical and emotional symptoms are not fully understood [42]. Elevated concentrations of peripheral inflammatory markers such as CRP and IL-6 have been linked to ELS in longitudinal cohort studies of healthy community samples [43] and depressed patients [44] alike.

Low-grade inflammation is increasingly being identified by researchers as an important potential determinant of many common medical disorders and disease states, including obesity, metabolic syndrome, diabetes, atherosclerosis, and depression [45–47]. While statistical correlations between various measures of

Table 11.1 Animal models used to study consequences of stress exposure

Type of experimental stressor	Clinical phenotype
Mechanical/thermal	Hyperalgesia, allodynia
Social dominance/predator threat	Psychosocial stress
Neonatal maternal separation/deprivation	Childhood abuse/neglect
Injection of foreign substance	Focal inflammation
Unpredictable sound	Chronic environmental stress
Physical restraint	Chronic intermittent (nonspecific) stress
Brief intermittent stress exposure	Arousal regulation/resilience

stress, inflammation, and chronic pain may be fairly reliably detected in human samples, experiments conducted in preclinical laboratories are invaluable for closer scrutiny of the knowledge gaps, such as biological mechanisms of ELS.

Animal Models of Stress and Pain

To elucidate the mechanisms underlying pathophysiological processes, chronic pain researchers rely on laboratory-based methods. However, chronic pain research is hampered by the same issues as those afflicting research into other chronic disorders—pain disorders have complex clinical phenotypes, and most diagnoses are pursuant to patient self-report [48]. Laboratory models must rely on observations of an animal's behavioral response to a particular nociceptive stimulus. Combining a nociceptive stimulus, such as an injection of formalin, with an environmental stressor, such as cold, sound, or separation of a young animal from its mother, may enhance some animal stress paradigms and generate results more comparable to human pain syndromes [49]. Examples of different experimental stressors employed in preclinical research and the associated phenotypes observed in human subjects are listed in Table 11.1.

Findings from animal studies are instructive in exploring the mechanisms and other factors that determine duration or chronicity of a painful or pain-sensitive state. For example, in a model of fibromyalgia-type widespread pain, intermittent exposure to noxious sound, combined with sympathoadrenal activation via epinephrine injection, induced mechanical hyperalgesia in mice for 28 days following the initial stress exposure [50]. Another experiment showed that mice exposed to intermittent, but not continuous, delivery of a cold stressor developed sustained thermal hyperalgesia that lasted 12 days following the stress period [51]. A third type of laboratory stressor, physical restraint intermittently applied over a protracted period of time, has also reliably produced hyperalgesia and allodynia in rodent subjects [52]. Characteristics of the stress condition, such as acute versus chronic exposure, can be manipulated to elucidate variables required to initiate, amplify, or sustain pain and associated symptoms that appear similar to those seen in clinical samples.

Throughout the life cycle, stress is associated with exacerbation of disease states. However, timing of stress exposure, relative to the developmental timing of brain and other organ functions, may be a particularly important determinant of future health consequences [53, 54]. Animal models like those described above have been used to examine the influence of ELS on various aspects of pain response [54–56]. For example, female rat pups separated from their mothers for 3 h per day displayed relatively heightened pain sensitivity later in life [57]. Early maternal separation has also been shown to reduce analgesic effects of morphine in laboratory animals, a feature often observed in chronic pain patients [58]. In a study comparing maternally reared and artificially reared (stressed) rats, researchers observed greater baseline pain sensitivity, and more paw inflammation after injection with saline, in subjects deprived of maternal care [59]. Repeated maternal separation has been shown to increase not only the nociceptive response but also the affective response to pain (measured by time the animal spends tending to the painful area) [60]. While a comprehensive review is beyond the scope of this chapter, preclinical research methods for studying the effects of stress and ELS have generated numerous findings suggesting common biological mechanisms behind the development of chronic pain syndromes and the development of some behavioral changes consistent with human mood and anxiety disorders. Of the various chronic pain syndromes presenting in women, the mechanism of pathology along the trajectory from ELS to onset of visceral hyperalgesia in adulthood is among the best understood at this time.

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain, discomfort, and altered bowel motility. By definition, IBS is a functional disorder and is currently diagnosed only in the absence of identifiable organic causes for the presenting symptoms [61]. IBS is typically diagnosed in adults between 20 and 40 years of age and is more common among women [62]. Once considered a purely psychosomatic condition, IBS is now recognized as a dysfunction of the brain-gut axis [63, 64]. The brain-gut axis is conceptualized as a superhighway of communication between the central nervous system and the enteric nervous system. Animal models of stress show that the breakdown of the brain-gut axis function precipitated by stress and perpetuated by immunological changes is the most likely culprit in the development of the disorder (see review, [65]).

IBS has long been considered a disorder of psychological origin because women with the diagnosis are more likely to report psychosocial stress, compared to women suffering from other gastrointestinal disorders [66]. Furthermore, childhood maltreatment and other types of ELS have been closely linked with the development of IBS, particularly in women [3, 67, 68]. Abnormalities of HPA axis function observed in IBS samples are similar to those reported for patients with mood and anxiety

disorders [69, 70] and for healthy community samples with ELS [71, 72]. Recent investigations into peripheral markers of immune function illuminate the role that immune system abnormalities play in shaping the underlying pathology of the IBS, particularly when comorbid with stress and anxiety [65, 73–76].

Models of stress in preclinical IBS research are predicated on replication of the phenotypes expressed by those with the disorder, and though the validity and utility of animal models for such a complex clinical syndrome are debated [48], preclinical research methods provide important insights into the etiopathology of IBS [77, 78]. Maternal separation or deprivation stressors have proven particularly effective methods for laboratory studies of gastrointestinal function changes relevant to IBS. Daily separation of rodents from their mothers for 3 h (during postnatal days 2–14) was associated with increased visceral hyperalgesia and increased brain and spinal cord expression of c-fos (a gene marker of neuronal activity) when the subjects experienced noxious colorectal distention [79], suggesting specific neural pathways being turned on or upregulated during visceral discomfort. Maternal separation has also been associated with relatively lower pain threshold and with subsequent changes in production of serotonin in spinal cord and colon [80]. ELS in the form of early maternal deprivation increased several measures of stress reactivity and immune system response, increased visceral sensation, and produced changes in gut microbiota as apparent consequences of the stressor [81].

A more direct link between maternal separation and immune mechanisms underlying IBS was demonstrated in a study of IL-6 activation of the enteric nervous system in rat colon [82]. Adult rats subjected to maternal separation (MS) had elevated circulating levels of IL-6 as compared to normally reared (NS) rats. Mucosal cells from MS rats produced more IL-6, and expression of IL-6 receptors in colonic tissue was significantly increased after exposure to mucosal secretions (when compared to NS rat tissue). IL-6 also activated cellular signaling pathways in submucosal glia, a key step in cytokine production. An even more interesting finding was that IL-6 increased influx of calcium in submucosal neurons of the colon, thus mediating an excitatory process that may, in the intact bowel, contribute to increased motility and pain observed in IBS patients. In fact, these results suggest that ELS (maternal separation) initiates a positive feedback loop: maternal separation induces increased IL-6 production by mucosal cells, which leads to increased production of IL-6 by submucosal glia, which subsequently binds to IL-6 receptors on nearby enteric neurons, resulting in IBS symptoms. The stress induced by these symptoms likely triggers increased IL-6 production and, thus, intensification of the abnormal response of the enteric nervous system.

Of potential relevance for development of novel therapeutics, reversal of visceral hypersensitivity could be demonstrated through blockade of serotonin type 2B receptors [83]. Exposing maternally deprived rates to different types of acute stressors in adulthood produced differential patterns of CRF receptor expression in the colon [84] along with evidence of several morphological changes in colonic tissues itself, particularly in animals displaying high levels of anxiety-like behaviors. Thus, the experience of ELS not only leads to functional abnormalities of the gut but also contributes to anatomical changes reflecting damage to the colon itself.

Multiple lines of evidence have identified immune function as the link between ELS and development of IBS [4]. In clinical samples, ingestion of probiotic foods containing a bifidobacterium strain is associated with reduction of symptoms concurrent with increased anti-inflammatory cytokines and reduced proinflammatory cytokines in peripheral blood samples [85]. Colon biopsies from IBS patients show increased mucosal immune cells (CD3+, CD4+, and CD8+ T cells and mast cells) [86]. Laboratory animals exposed to ELS show alterations in the balance of colonic microflora and enhanced immune reactivity to bacteria challenge [81] akin to those noted in IBS, and ELS animals have been found to have increased cytokine mRNA expression and mast cell density in the colonic epithelium [4], relative to non-stressed controls. Increased lesions of the mucosal barrier and greater colonic permeability observed in ELS subjects [87] suggest a mechanism that permits entry of inflammatory bacteria into the colonic lumen in IBS patients. Stress may also exert immune effects on the gastrointestinal tract via recognition molecules of the innate immune system called "Toll-like receptors" (TLRs) [88] and "Nod-like receptors" (NLRs) [89, 90]. When activated by bacteria or viruses in the gut, TLRs and NLRs provide signals to elicit antigen-specific immunity in the local tissue microenvironment through nuclear factor kappa-light-chain-enhancer of activated B cells (abbreviated as "NF-κB") and inflammatory cytokine expression.

While the link between immune function and early life stress in the development of IBS is not as readily demonstrated in humans as it is in animal models, associations between IBS and immune system activation are clear in studies with clinical samples. In a study of HPA axis reactivity and associated release of proinflammatory cytokines, all subtypes of IBS patients were found to have elevated concentrations of IL-6, soluble IL-6 receptor, and IL-8 [91] in peripheral plasma samples. A study of inflammatory cytokine production in peripheral monocytes found higher baseline levels of TNF-alpha, IL-1beta, and IL-6 in IBS patients than controls [73], and analysis of those data by IBS symptom subtypes revealed that diarrhea-predominant IBS was associated with higher cytokine levels overall, relative to constipation-predominant subtypes or healthy controls. Another investigation of plasma cytokine profiles also demonstrated elevated IL-6 and IL-8 levels in women with IBS relative to matched controls; in that study, the subset of patient with IBS and comorbid fibromyalgia (FM) or chronic fatigue syndrome (CFS) showed significantly elevated TNF-alpha and IL-1beta levels [76]. Taken together, these clinical data have added to the current acceptance of immune mediators as critical facilitators in the pathophysiology of IBS [78].

Fibromyalgia (FM)

Like IBS, fibromyalgia (FM) is considered a functional pain disorder. According to the formal diagnostic criteria established by the American College of Rheumatology (ACR, 1990), an individual with FM must have chronic, widespread musculoskeletal pain for at least 3 months and experience pain on palpation at 11 of 18 tender

points located on the body [92] (see Chap. 3). In addition to chronic pain, FM patients often describe overwhelming fatigue, sleep abnormalities, and mood disturbance [93]. Women are more likely than men to be diagnosed with FM according to ACR criteria [94], and they are nine times more likely to seek treatment for FM-related symptoms [95]. Given the high prevalence of reported ELS among patients with FM [96, 97], stress reactivity has been investigated as a potential mediator between adverse early environment and abnormal brain development, ultimately leading to onset of an FM syndrome [5].

Dysfunctional pain processing within the central nervous system is thought to be the salient mechanism leading to hypersensitivity to pain in FM [98–102]. Dysregulation of pain processing may be modulated by the HPA neuroendocrine axis such that hypoactivity of the HPA response to acute stress (i.e., insufficient acute release of cortisol) prevents normal restraint of the proinflammatory immune response in FM [103, 104]. While symptoms of FM are themselves not considered to be inflammatory in nature [105], cytokines and the inflammatory immune response may still play a role in the pathophysiology of the disorder. Evidence of this was first derived from studies that found elevated levels of immune markers in FM patients [106, 107]. More recent work suggests that the heightened levels of circulating proinflammatory cytokines (IL-1beta, TNF-alpha, and IL-6) in FM are independent of body mass index [108]. Not all studies have replicated these findings when comparing cytokine profiles of FM and control groups [109], but there is consistent support for the conclusion that proinflammatory cytokines IL-1, IL-6, and IL-8 are dysregulated in FM and contribute to some of the ancillary symptoms of the disorder such as fatigue, sleep disturbances, cognitive deficits, and depression [110].

One study of individuals with chronic widespread pain (including many with FM) found reduced expression of anti-inflammatory cytokines IL-10 and IL-4 in patients, relative to controls [111]. The inconsistent patterns observed across studies have not clarified the role of cytokine activation on the neuroendocrine-immune response patterns in persons with FM, and specific mechanisms by which pro- and anti-inflammatory cytokines produce or interact with other components of pain processing symptoms in FMS remain elusive [40, 112] despite preclinical research efforts. As such, cytokines are not considered reliable biomarkers for FM at this time [113].

Implications for Clinical Practice

Knowledge about the intimate and well-established relationships between stress, immune system function, and chronic pain syndromes can benefit healthcare in numerous ways. When collecting history of events and symptoms associated with the presenting concern, clinicians should routinely query their patients about childhood abuse, neglect, or other forms of stress in the neonatal and prepubertal stages of life. When conducting a review of systems, the presence or past history of other chronic pain syndromes and/or psychiatric symptoms should be ascertained, as such

history may yield additional evidence of an inflammation-mediated pathology relevant to the presenting pain, to comorbid health disorders, and to course of symptoms over time. For example, recent evidence shows that ELS is associated with chronification of migraine [114] and that the link between early life environment and adult pain is strongest among patients with multiple pain conditions and reporting multiple types of ELS (abuse or neglect that was physical, sexual, or emotional in nature) [2]. The clinicians familiar with the evidence base can confidently communicate their knowledge base both implicitly and explicitly during clinical interactions, so the patient does not feel blamed, shamed, or otherwise inhibited in reporting her symptoms and seeking appropriate care.

Both patient and clinician should be sufficiently educated about maldynia—maladaptive pain that does not promote healing/tissue repair and occurs in the context of no obvious noxious stimulus—to appreciate it as a chronic disorder of the CNS sensory- and emotion-processing functions. A basic understanding of the biological basis of chronic pain and a mastery of basic concepts related to triggering, perpetuation, and extinction of symptoms are likely to foster a sense of empowerment in the patient. Such empowerment may in turn enhance efforts to self-monitor and manage or reduce symptoms. Self-monitoring can be useful for identification of risk factors, for assessment of relevant symptom severity over time, and for prevention or care of broader health outcomes over time.

In light of the bidirectional relationships between stress and chronic pain syndromes in women, active management of current stress levels, perhaps with greater attention and commitment to relaxation, sleep, and use of health-promoting coping skills, may be one of the most important components of the treatment plan. The anti-inflammatory and other beneficial effects of regular exercise are well documented [115, 116]. Cognitive behavior therapy (CBT) can enhance pain control and reduce mitogen-stimulated levels of interleukin-6 (IL-6) [117], and the practice of meditation has been shown to reduce both psychological distress and cytokine response when confronted with acute stress challenge [118]. In addition, increased exposure to mentally stimulating environments and physical activity has been shown to improve immunity and extend longevity in animal studies [119]. Targeted strategies to address specific stressors in a patient's daily routine may prove critical for implementing behavior changes necessary for improved health outcomes.

In studies of major depression, ELS has been found to mediate both short- and long-term treatment outcomes, with psychotherapy emerging as particularly important intervention in combination with medication [120, 121]. While clinical trials have not yet determined whether chronic pain syndrome patients with a history of ELS will respond the same as those without ELS when currently available pharmacotherapy is administered [68], there is general consensus that multimodal and custom-tailored treatment plans produce the best outcomes for these patients [122, 123]. In the future, recognition of the important role ELS plays on the developing immune system and, in turn, on nociceptive hypersensitivity will likely lead to the use of more ELS animal models in development of more specialized treatments for women with chronic pain syndromes [124].

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Chapter 12
Menopause and the Musculoskeletal System

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Introduction

Estrogen is a known regulator of both bone and muscle. Estrogen withdrawal, either iatrogenic or due to menopause, has a profound impact on the musculoskeletal system. Reductions in muscle power, strength, and endurance as well as accelerated bone turnover and increased fracture risk lead to increased morbidity and mortality.

Definition and Diagnosis of Osteoporosis

Osteoporosis is a disease that affects more than 55% of Americans over the age of 50 [1]. The National Osteoporosis Foundation estimates that one half of all women over the age of 50 will experience an osteoporotic fracture in their lifetime. Twenty percent of ambulatory individuals require long-term care following a hip fracture with a 1-year mortality rate as high as 24% [2]. Osteoporotic fractures result in disability, decreased independence, and premature death. In fact, more American women die each year due to complications following an osteoporotic fracture than due to cancers of the breast and cervix combined. The estimated national direct

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expenditure (costs associated with hospital and nursing home care) for osteoporosis and associated fractures is $13.8 billion ($38 million/day), and the cost is rising.

Osteoporosis is characterized by low bone density, poor bone quality, and increased fracture risk. Dual-energy X-ray absorptiometry (DXA)-derived T-scores are used clinically to estimate fracture risk based on bone density values for postmenopausal women or men and women aged 50 or older. Osteopenia (T-score −1 to −2.5) is defined by the World Health Organization (WHO) as bone density between 1 and 2.5 standard deviations below a young adult reference population. Osteoporosis (T-score less than or equal to −2.5) is defined as bone density equal to or greater than 2.5 standard deviations below a young adult reference population. Severe or established osteoporosis is defined as a history of low-impact fracture and a bone density equal to or greater than 2.5 standard deviations below a young adult reference population. In postmenopausal women or those age 50 or greater, osteoporosis can be diagnosed based on a history of low-impact fracture alone. Z-scores are used for men and women under the age of 50 to compare bone density to an age-matched reference population. A Z-score more than 2 standard deviations below the reference population is indicative of bone density less than expected for age and gender. A diagnosis of osteoporosis cannot be made based on Z-score. The FRAX tool (www.shef.ac.uk/FRAX), developed by the WHO, estimates the 10-year risk of a major osteoporotic fracture based on clinical factors (age, gender, height, weight, parent history of fracture, personal history of fracture, smoking status, alcohol use, steroid use, history of rheumatoid arthritis, history of secondary osteoporosis, and bone density at the femoral neck). Based on the FRAX algorithm, treatment is recommended for postmenopausal women with a history of hip or vertebral fracture, a T-score ≤−2.5 at the femoral neck or spine, low bone density and a 10-year probability of hip fracture ≥3%, or a 10-year probability of a major osteoporosis-related fracture ≥20%. The U.S. Preventive Services Task Force recently revised DXA screening recommendations [3]. All women aged 65 and older should be screened for osteoporosis by DXA scanning. Additionally, women under the age of 65 with a FRAX determined 10-year major osteoporotic fracture risk that is greater than 9.3% should also undergo DXA testing for osteoporosis screening. The task force made no recommendation for osteoporosis screening in men due to lack of evidence.

Estrogen Withdrawal and Bone Loss

Osteoporosis may be primary type 1 (postmenopausal), primary type 2 (age related and twice as common in women as men), and secondary (due to drug use or another medical condition resulting in abnormal bone metabolism, equally common in men and women). Postmenopausal women may experience bone loss due to a combination of sex steroid withdrawal, advancing age, and medical conditions associated with bone loss. Bone homeostasis is normally maintained by the tightly coupled

activity of bone-resorbing cells (osteoclasts) and bone-forming cells (osteoblasts). With advancing age, bone resorption proceeds in excess of bone formation leading to a net loss of bone. Age-related bone loss is also attributable to the reduced capacity of mesenchymal stem cells within bone marrow to differentiate into bone-forming cells. Bone marrow is found in the medullary cavity of long bones and is composed primarily of mesenchymal stem cells, hematopoietic precursors, and marrow fat. Bone and fat cells arise from the same mesenchymal precursor stem cell within the bone marrow, capable of differentiation into osteoblasts or adipocytes under the control of transcription factors such as the peroxisome proliferator-activated receptor-γ (PPAR-γ) [4, 5]. Mesenchymal stem cells are depleted and become more likely to differentiate to adipocytes over osteoblasts with aging. As a result, bone marrow fat increases with age. Increased marrow fat content has been associated with decreased trabecular bone volume [6], bone density [7], and decreased bone strength [8, 9]. Fatty marrow conversion contributes to age-related bone fragility and fractures [10] and is seen in other disorders characterized by low bone mass, including anorexia nervosa [7]. Inactivity and microgravity also deplete the mesenchymal stem cell population within the marrow [11] and suppress osteoblastogenesis [12].

In adult women, bone density is stable until the age of 30 and then declines by roughly 1% per year until stabilizing again 4–5 years following the onset of menopause [13]. Estrogen is known to protect the adult skeleton against bone loss via mechanisms that have not been fully elucidated [14]. One mechanism involves the suppression of levels of inflammatory cytokines within the bone microenvironment. Estrogen withdrawal leads to increased levels of cytokines that upregulate osteoclastogenesis, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 [15]. Bone resorption following estrogen reduction might also be attributed, in part, to reduced antioxidant defenses in osteoclasts and/or other cells in the bone marrow. Free radicals are involved in the pathogenesis of osteoporosis [16], and there is increasing evidence supporting a role for free radicals in the osteoprotective activity of estrogen. In other tissues, estrogen is known to suppress the generation of reactive oxygen species (ROS) [17–19]. At the cellular level, ROS have been found to stimulate osteoclastic bone resorption [20, 21] and osteoclast differentiation [22, 23], whereas free radical scavengers and antioxidants inhibit osteoclast activity. Antioxidants regulate bone mass in vivo as well. Ovariectomy in mice leads to a substantial reduction in the levels of the main thiol antioxidants, glutathione and thioredoxin [21]. Conversely, levels of both antioxidants as well as their regenerative enzymes are rapidly normalized by a single injection of 17-β estradiol [24]. Treatment with antioxidants prevents estrogen-deficiency bone loss, while drugs which result in reduced thiol antioxidants, like buthionine sulfoximine (BSO), induce bone loss. Dietary antioxidants [25, 26], levels of plasma antioxidants [27, 28], and oxidative stress [29] have been all linked to bone mineral density status and risk of hip fracture. These findings suggest that estrogen deficiency causes bone loss, in part, by lowering antioxidant levels in bone. The presence of estrogen, on the other hand, may prevent bone loss by enhancing bone antioxidant defenses.

Other Factors Contributing to Osteoporosis in Postmenopausal Women

Recent studies have demonstrated an important physiologic link between bone and fat [30–32]. Obesity is widely considered to be osteoprotective, i.e., persons with a greater BMI are less likely to have osteoporotic fractures [33–35]. Some reports in the literature suggest increased fractures in obese adults [36] and obese children [37]. Furthermore, obesity in adolescence causes decreased bone strength relative to body weight [38]. The impact of obesity on bone is multifactorial and may involve multiple pathways that influence both bone formation and resorption with competing effects on the skeleton. One such pathway involves adipocyte production of hormones that are known regulators of bone metabolism. Leptin is one example of a bone-regulating hormone produced primarily by adipocytes. Leptin was originally described as the product of the obesity gene. It is known to regulate energy expenditure and appetite via binding to its receptor in the arcuate nucleus of the hypothalamus. This binding triggers sympathetic regulation of energy expenditure in the periphery. The observed link between obesity and bone mass led to the investigation of leptin's role in bone metabolism. Several lines of evidence suggest leptin signals via central and local pathways to regulate both bone formation and bone resorption. The mechanism of central control of bone is similar to but distinct from the hypothalamic relay controlling appetite [39]. The downstream target of this pathway is the beta-2 adrenergic receptor expressed on the surface of osteoblasts. Signaling via this pathway results in leptin-induced suppression of bone formation by sympathetic inhibition of osteoblast activity [40]. Within the bone microenvironment, the leptin receptor is expressed on osteoblasts [41] and has been shown to promote osteoblast over adipocyte differentiation in bone marrow stromal cells [42]. Leptin has also been shown to inhibit in vitro differentiation of human peripheral blood mononuclear cells (PBMC) into mature, functional osteoclasts. Leptin may suppress osteoclast differentiation via a target cell within the PBMC population. Therefore, leptin can itself have competing effects on bone metabolism depending upon the signaling pathway. Similarly, adiponectin is a polypeptide hormone produced by osteoblasts and by adipocytes in both visceral and marrow fat depots. Active adiponectin receptors are expressed on bone cells [43] and, although adiponectin levels are typically inversely related to the degree of adiposity, elevated levels of adiponectin have been associated with bone loss in both men and women as well as in rodent studies [30–32, 44–53]. Elevated serum levels of both leptin and adiponectin have been associated with accelerated bone loss.

A second pathway linking bone to fat involves increased mechanical loading that stimulates bone formation. The protective effect of obesity on bone may be attributable to the increased mechanical loading of bones during ambulation. The discovery of the role of Wnt signaling pathways in bone homeostasis has radically transformed our understanding of the cellular and molecular mechanisms responsible for the adaptation of bone to mechanical loading [54, 55]. Osteocytes, the cells responsible for mechanotransduction in bone, represent the first cellular response to unloading [56].

Sclerostin and Dkk1 are two secreted Wnt signaling antagonists produced by osteocytes. These two molecules can selectively inhibit Wnt/β-catenin, suppressing the activity of osteoblasts, as well as the viability of osteoblasts and osteocytes. Mechanical unloading causes upregulation of both Sclerostin and Dkk1, leading to reduced Wnt/β-catenin signaling in osteoblasts. The currently accepted paradigm states that Wnt binds to a coreceptor complex involving Frizzled receptor and low-density lipoprotein receptor-related protein (LRP)-5 or LRP-6, both present on osteoblasts. This binding stabilizes cytoplasmic β-catenin and causes it to translocate to the nucleus. Translocation of β-catenin, in turn, activates the transcription of genes that promote osteoblast proliferation, differentiation, and function, ultimately resulting in new bone formation. Several antagonists have been described that can inhibit this signaling pathway. For instance, molecules like secreted Frizzled-related proteins, Wif (Wnt inhibitor factor), and Cerberus can bind Wnt and functionally block the pathway. Dickkopfs (Dkk1) and Sclerostin, on the other hand, inhibit the Wnt pathway by preventing the formation of the Wnt-Frizzled-LRP5 complex by promoting the internalization of the LRP5/6 coreceptor (Dkk1) or by competitive binding to LRP5 (Sclerostin) [57, 58]. Dkk1 and Sclerostin are produced primarily by osteocytes. Sclerostin, encoded by the *SOST* gene, is a potent inhibitor of bone growth [59–61]. Dkk1 is an osteogenesis-inhibiting factor that mediates bone loss in several physiological and pathological contexts [62–65]. In addition to its effect in osteoblasts, Dkk1 signaling can also inhibit chondrogenesis during new bone formation and mediate chondrocyte apoptosis in the osteoarthritic joint [66].

Several elegant animal studies have shown that Dkk1 and Sclerostin levels are inversely proportional to bone mass [60, 67] and that production of Sclerostin and to a lesser extent Dkk1 by osteocytes is dramatically reduced by mechanical loading in rats and mice [68–70]. Postmenopausal women have significantly higher serum Sclerostin levels [71], and serum Dkk1 levels were found to be significantly higher in osteoporotic women compared with women with normal bone density [72]. The literature to date reports changes in circulating levels of Sclerostin or Dkk1 in response to PTH administration in osteoporotic women.

The contribution of lean mass to bone remodeling is not fully understood; however, it has been suggested that mechanical loading must be dynamic, or occur in conjunction with muscular contractions, to be osteogenic [73, 74]. Mechanical stimulation of bone, either via dynamic mechanical loading or via low-magnitude mechanical signals (LMMS), has great therapeutic potential to treat osteoporosis. Low-magnitude mechanical signals (LMMS) have been shown in both human and rodent models to promote new bone formation as well as decrease dietary-induced obesity [75]. Rodent models of mechanical loading have contributed greatly to the understanding of the osteogenic response to mechanical strain. Atypical strain patterns are most effective at generating an osteogenic response [76]. The magnitude of force applied and the frequency of loading are also important determinants of the response to dynamic loading [77]. Bone cells rapidly become desensitized to prolonged loading, and therefore, periods of rest are required between sessions to maximize osteogenic potential [78–80]. While these findings have been reported extensively in the basic literature, the principles have not always been applied to

exercise training programs aimed at treating or preventing osteoporosis. Ideally, the optimal weight-bearing exercise would rapidly deliver a high loading force in an unusual distribution with sufficient rest between training sessions to minimize decreased mechanosensitivity.

Treatment Options for Osteoporosis: Weight-Bearing Therapies

Given the importance of mechanical strain as a regulator of bone metabolism, weight-bearing therapies have great potential to prevent or treat osteoporosis. While it is commonly accepted that weight-bearing exercises are osteoprotective, there is no consensus regarding the type, duration, or intensity of exercise that will slow or reverse bone loss in postmenopausal osteoporosis. The rate of bone loss in early, healthy menopause varies according to skeletal site. A decrease of 1.5% per year is typical at the lumbar spine with 1.2% per year common at the femoral neck. This rate slows within 4–5 years following the onset of menopause [13]. To be considered beneficial, a training program would at least counter the 1–1.5% bone loss expected in the early stages of estrogen withdrawal. Several studies have assessed bone response to various training programs in postmenopausal osteoporosis. In a 2-year longitudinal trial, Kerr et al. studied the effect of exercise and calcium supplementation on BMD in 126 postmenopausal women. Participants were assigned to one of three groups; strength training, endurance training, and nonexercise. They found strength training increased hip BMD by roughly 1% in a site-specific and load-dependent manner. No gains in BMD were found at the L-spine, radius, or whole body due to strength training. BMD was decreased in the other two groups at all sites tested [81]. In studying the effects of a 1-year walking program with calcium supplementation on BMD in postmenopausal women, Nelson et al. found daily supplementation with high levels of calcium (831 mg) resulted in a 2% increase in BMD at the femoral neck. Exercise was thought to be noncontributory to this increase. In a subsequent study, they report a 1% increase in L-spine and femoral neck BMD following a 1-year high-intensity strength-training program. The Erlangen Fitness Osteoporosis Prevention Study (EFOPS), an ongoing 5-year exercise trial in early postmenopausal osteopenic women, found mixed high-intensity exercise prevented BMD loss at the L-spine and hip. Participants were assigned to an exercise group or to a control group that did not exercise. The participants in the control group lost a significant amount of BMD at both skeletal sites despite maintaining a stable muscle mass and strength. While lower extremity strength is a determinant of fracture risk, preservation of strength is not sufficient to prevent bone loss [82, 83]. Cumulatively, these studies suggest weight-bearing exercises are effective for preventing bone loss but do not restore BMD lost due to postmenopausal osteoporosis.

While BMD is often used to assess fracture risk, it is a surrogate for bone strength. It has been suggested that bone responds to loading by increasing cortical bone at the site of greatest mechanical strain [80]. In a rodent model, a 5.4% increase in BMD correlated to a 64% increase in bone strength (reported as force to failure).

For this reason, dual-energy X-ray absorptiometry (DXA) may not be the most sensitive tool to monitor increases in bone strength and changes in fracture risk in response to weight-bearing exercises. Quantitative computed tomography (QCT) has the advantage of separating cortical from trabecular bone measurements and reporting each individually. Changes in BMD at the L-spine in response to exercise were assessed by DXA and QCT at year 3 of the EFOPS. While no improvement was found by DXA, a 5% gain in cortical bone was found only in the exercise group [84]. With this in mind, prior studies that report minimal or no change in BMD by DXA may actually underestimate the effects of exercise on bone strength and by extension fracture risk.

Osteoporosis Medications

In addition to weight-bearing exercises, medications are often prescribed to increase bone density and reduce fracture risk. Bisphosphonates are the most commonly prescribed class of medication to treat osteoporosis. The following are FDA approved to treat or prevent postmenopausal osteoporosis and have been shown to reduce fracture risk: Fosamax (alendronate), Actonel (risedronate), Boniva (ibandronate), and Zoledronic acid (to treat postmenopausal osteoporosis only, not FDA approved for prevention). Normal serum levels of vitamin D may be required to optimize the efficacy of bisphosphonate therapy [85, 86]. Bisphosphonate medications suppress bone resorption by promoting osteoclast apoptosis. They therefore reduce bone resorption but have limited effect on bone formation. Because bisphosphonates specifically target osteoclasts, they can also reduce coupled bone remodeling since bone formation by osteoblasts requires osteoclastic bone resorption. Abnormal bone remodeling with poor bone quality and impaired capacity to heal microcracks may result in atypical thigh fractures reported in long-term bisphosphonate use [87–89]. Bisphosphonate therapy is associated with osteonecrosis of the jaw in individuals undergoing dental procedures. Oral administration can cause or exacerbate esophagitis or gastritis and should not be prescribed to people with underlying esophageal abnormalities (strictures, achalasia). More recently, bisphosphonate use was identified as a risk factor for atrial fibrillation in women [90–93].

Teriparatide (Forteo) is an anabolic bone medication FDA approved to treat osteoporosis in men and women with a high fracture risk (previous fractures, multiple fracture risk factors). This is a recombinant parathyroid hormone and has been shown to stimulate osteoblast activity, thereby increasing bone formation, increasing bone mass, and decreasing fracture risk [94–97]. It is administered once daily as a subcutaneous injection. Teriparatide is known to cause osteosarcoma in rats and is therefore not recommended for individuals at risk for developing osteosarcoma (history of bone cancer or metastasis to bone, history of radiation therapy to bone). Denosumab (Prolia) is an anti-RANKL antibody that inhibits osteoclast formation by binding RANKL, thereby preventing osteoclast activation. Denosumab is FDA approved to treat postmenopausal women with osteoporosis at high risk for fracture

(previous fractures, multiple fracture risk factors). Clinical trials are under way to test the efficacy of an anti-sclerostin antibody (AMG 785) to treat postmenopausal osteoporosis. Estrogen and selective estrogen receptor modulators increase bone mass and decrease fracture risk. However, these are drugs that are more frequently prescribed for other medical conditions with the added benefit of an osteogenic effect. Fluoride and calcitonin are other medications that are less frequently prescribed to treat or prevent osteoporosis. Maintaining adequate dietary intake of calcium and vitamin D is essential to prevent exacerbation of postmenopausal osteoporosis. The National Osteoporosis Foundation recommends 1,200 mg of calcium and 800–1,000 international units (IUs) of vitamin D each day for women over the age of 50. The Institute of Medicine (IOM) recently released a statement on calcium and vitamin D intake and defined normal serum 25 OH vitamin D levels as 20 ng/mL or greater [98].

Estrogen and Muscle

While maintaining bone mass is an important strategy for preventing osteoporotic fractures, improving lower extremity strength may also have therapeutic value in fall prevention and fracture risk. Skeletal muscle cells express estrogen receptors (ER). ERα and ERβ mRNA and receptors are present in skeletal muscle tissue of human subjects regardless of gender [99–102]. ERα expression is an order of magnitude greater than ERβ expression, with roughly 75% of the ER's residing within muscle cell nuclei and the remainder within the capillary endothelium [100–102]. A third estrogen receptor, G-protein-coupled receptor 30, was recently identified in murine skeletal muscle [103].

The presence of ERs in skeletal muscle nuclei suggests that estrogen levels may influence skeletal muscle phenotype or function. However, unlike its well-characterized impact on the skeletal system, the role of estrogen in skeletal muscle physiology is less well defined and, in several aspects, controversial. In this section, we briefly review what is known about the effect of estrogen on skeletal muscle function. While our focus is on a role in human physiology, when appropriate, we address animal models, isolated tissue preparations, and cellular preparations.

Muscle Strength

In the mid-1970s, it was observed that while handgrip strength decreased with age, for women, the major decrement occurred around age 50, suggesting that some relationship existed between menopause and muscular strength [104]. In a very influential paper, Phillips and colleagues confirmed that many, but not all, postmenopausal women were weaker than age-matched males [105]. Most importantly, postmenopausal subjects receiving estrogen therapy had strength per muscle cross-sectional area equivalent to that of their male peers. In a subsequent intervention

trial, this same group reported that 1 year of hormone therapy (HT) increased strength by 12% in postmenopausal women compared to a 3% decline for nonusers [106], and over the next 4 years, those subjects who stopped therapy showed a reduction in strength in comparison to those who continued with HT [107].

These early studies stimulated investigations into the relationship between muscle strength and estrogen in both pre- and postmenopausal women. This work is not without controversy. For instance, in young women, strength was reported to be ~10% greater at the midpoint of the ovulatory cycle, when estrogen peaks, compared to the remainder of the cycle [105, 108]. This monthly variation in strength was present in both athletic and nonathletic populations but absent in women taking oral contraceptives and in male subjects. However, these results were not confirmed in another group of young women [109]. This study examined only three time points during each cycle, and more time points may be required to detect the rather small, but abrupt, change in force observed by others. Finally, no change in strength was observed in women receiving gonadotrophin injections during in vitro fertilization treatment, which increased estrogen levels to supraphysiological levels [110]. This suggests that other hormones that change during the menstrual cycle, such as progesterone, follicle-stimulating hormone, or luteinizing hormone, may interact with estrogen to influence strength.

Likewise, a number of subsequent studies of HT on muscle strength have supported a role of estrogen and muscle strength [111], while other studies have not [112, 113]. In one of the more recent studies, utilizing 15 pairs of monozygotic twins discordant for HT use, no difference in isometric knee extension strength between hormone users and nonusers was reported [114]. To clarify this issue, Greising et al. [115] reviewed 23 human hormone therapy studies and found that when all muscles were examined together, there was a positive, but small (5%), effect of estrogen therapy on strength. The adductor pollicis benefited the most from hormone therapy (+17%). The adductor pollicis is also one of the muscles reported to show fluctuations in strength during the menstrual cycle [105]. These points may be significant in terms of understanding the literature. The use of the adductor pollicis reduces several confounding variables, such as skill and motor unit activation, that may be present when larger muscles, such as those of the lower limbs, are studied [105]. Methods are also available for reliability measuring the cross-sectional area of the muscle [116]. Because the effect of estrogen on strength is modest at best, strength changes with naturally fluctuating estrogen levels or with estrogen therapy may get lost in the methodological and physiological "noise" present when larger muscles are studied.

Another experimental approach for reducing some of the issues that may confound measurement of human muscle strength is to utilize isolated muscle preparations from animal models. Studies of ovariectomized (OVX) rats have shown little consistent effect of a lack of estrogen on peak tetanic force [117, 118]. In contrast, studies on mice have revealed strong relationships between estrogen and muscle function. In mice allowed to age, a 25% decrement in soleus peak tetanic force occurs at approximately the same time as ovarian senescence [119]. However, unlike humans, estrogen treatment does not restore soleus force after ovarian senescence [120], suggesting a loss of estrogen sensitivity with age in this particular species.

Young OVX mice show a 10–18% reduction in soleus and EDL tetanic force expressed per unit muscle mass when measured in vitro [121, 122]. This force deficit is prevented in OVX mice treated with estradiol [122]. In fact, when sham, OVX, and OVX-estradiol-treated mice are analyzed together, a significant positive relationship was observed between soleus force and plasma estradiol concentration [122]. Finally, mice lacking ERα show an ~10–15% reduction in the in situ tetanic force per muscle cross-sectional area for the gastrocnemius and tibialis anterior [123]. While the soleus and plantaris were unaffected by the lack of this particular receptor, this experimental approach shows unequivocally that disruption of estrogen signaling leads to a modest reduction in force of some murine hind limb muscles.

Taken together, increases in strength at midcycle of the menstrual cycle and following hormone therapy fall in the 10–12% range. Similarly, reductions in muscle force in mouse models of OVX, and in mice lacking estrogen receptors, fall in a similar range. This suggests that estrogen has a modest, age-independent, direct effect on the muscular strength of women.

Muscular Power

Locomotion and other physical activities require muscles to not only produce force but to do so as they shorten. The ability to generate force while shortening can be quantified as muscular power, arguably the single most important contractile characteristic of skeletal muscle. Despite its functional importance, few studies have directly examined relationships between power and estrogen.

Assuming shortening velocity remains constant, then the modest increases in muscular strength discussed above would be expected to be associated with roughly proportional increases in muscular power. Lower body power, evaluated as vertical jumping height, was reported to be 20% greater for women receiving hormone therapy versus those not on therapy [114]. Interestingly, this power difference occurred in the absence of any detectable intergroup differences in isometric strength of the knee extensors. One possibility is that estrogen therapy increases the velocity of muscle contraction independent of any effects on muscle force. We consider this unlikely (see next section). An alternative explanation is that those on therapy were able to jump higher due to their almost 6 kg lower body mass compared to subjects not on HT. Alternatively, estrogen could impact neural recruitment and coordination of motor units, leading to increased jumping power without a subsequent increase in the force produced by the knee extensors.

Muscle Fatigue

Fatigue is defined as the failure of a muscle to maintain its expected force, shortening velocity, or power [124]. It is often observed that women exhibit less muscular

fatigue than men [125]. Likewise, isolated soleus and extensor digitorum longus muscles from female mice show greater fatigue resistance and quicker recovery than similar muscles from male mice [126]. What evidence is there that this gender difference is due to estrogen?

During the menstrual cycle, the knee extensors were reported to be most resistant to fatigue during the luteal phase or several days after estrogen and strength peaked [108]. Animal studies have also shown an antifatigue effect of estrogen. Oophorectomized rats treated with estradiol can run longer than nontreated animals [127]. This increase in endurance is at least partially due to an effect of estrogen on the muscle tissue as soleus muscles isolated from ovarian-senescent mice show less fatigue during stimulation when the animals had been supplemented with estradiol [120].

Potential Mechanisms

Fiber types. Skeletal muscle is a heterogeneous tissue, comprised of different cell types. Adult human skeletal muscles express three different fiber types based on their myosin heavy chain (MyHC) isoform expression: a "slow" type I isoform and the "fast" IIa and IIx isoforms (small mammals, like laboratory rodents, express a fourth fast MyHC isoform, type IIb). Modifications in MyHC isoform expression can influence muscle performance because fibers expressing the type I MyHC have a slower contractile velocity, slightly lower force per unit cross-sectional area, and substantially lower power output than fibers expressing the fast, type II MyHCs [128]. Muscles expressing predominately fast isoforms are also more fatigable than those expressing predominately slow isoforms. Thus, an important question is whether changes in fiber type composition are responsible for the observed effects of estrogen on muscle function and fatigue.

While OVX has been reported to shift the predominately slow rat soleus and the fast extensor digitorum longus towards slower phenotypes, the absolute changes are relatively small [129] and are not always observed [118]. In humans, no differences in histochemically identified fiber types, nor in the myosin heavy chain isoform expression of individual muscle cells, were observed between early postmenopausal women receiving or not receiving hormone therapy [130]. While more needs to be done, based on the available evidence, it is unlikely that the effects of estrogen on muscle contractility are due to myosin heavy chain or fiber type shifts.

Cross-bridge mechanisms of contraction. Reports that estrogen has a direct effect on force per unit cross-sectional area of muscle indicate that the quality of the muscle has been altered. This would occur if estrogen directly impacts the cellular and molecular mechanisms underlying contractility. One locus for such an effect would be at the level of the force-producing actomyosin cross bridges, and there is evidence to support this. In the absence of estrogen (OVX mice), the fraction of strong-binding myosin was reported to be 15% lower in isolated fast extensor digitorum longus muscles, consistent with the lower peak tetanic force of these muscles [121]. In OVX mice treated with 17-β-estradiol, the fraction of myosin heads in strongly

bound conformations was normalized [122]. The observation that OVX reduced the Ca^{2+}-activated force per cross-sectional area of skinned, or permeabilized, single fiber segments from the rat soleus [131] is also consistent with estrogen affecting the cross bridges. Thus, the absence of estrogen leads to a reversible reduction of actomyosin heads in the strongly bound, and hence force-producing, state of the cross-bridge cycle. While the exact mechanism by which this occurs is not clear, estrogen can alter the antioxidant status of the muscle cell [103], and muscle cells are sensitive to the redox status of their internal environment [132–134].

However, a study conducted on skinned fibers from postmenopausal women found no differences in peak Ca^{2+}-activated force, shortening velocity, or peak power of vastus lateralis fiber segments obtained from women on or not on hormone therapy [130]. This was observed for both the slow type I and the fast type II fibers. Why this work differs from the previously cited studies finding a link to the cross bridge is unclear. Potential explanations are that the sensitivity to estrogen at the level of the cross bridge varies between species or, alternatively, is lost during the aging process. For instance, oxidized proteins increase with age [135] and may overwhelm any antioxidant effects attributed to estrogen present at a younger age. The results of this work do not negate a role of estrogen on strength. However, these findings suggest that the mechanism responsible is not at the cross bridge in postmenopausal women.

Excitation-contraction coupling. An alternative, or complimentary, mechanism to explain the effects of estrogen on muscle force would be a force regulating event upstream from the cross bridge. There is no evidence that a lack of estrogen impacts the Ca^{2+} sensitivity of the thin filament, at least in slow fibers [131]. In contrast, muscle twitch kinetics, such as contraction time and relaxation time, which are partially a function of the sarcoplasmic reticulum's ability to release and resequester Ca^{2+}, appear to be estrogen sensitive [117, 118]. Cardiac muscle shows clear gender-based differences in Ca^{2+} handling. For instance, cardiac cells from female rats exhibit calcium transients that are smaller and slower, and Ca^{2+} sparks with smaller amplitudes and durations, than are observed in cardiac cells from male rats [136]. To our knowledge, similar comparative studies have not been conducted on skeletal muscles. It is noteworthy that excitation-contraction coupling impairment is a primary contributor to age-related muscle dysfunction [137], making restoration of this processes a potential mechanism behind the effects of hormone therapy on muscle strength. Further research could explore if hormone therapy restores excitation-contraction coupling in skeletal muscle and, if so, if this is related to improved skeletal muscle strength in postmenopausal women.

Cell energetics. In postmenopausal women, HT is associated with changes in a number of genes involved in energy metabolism. These changes include increased expression of genes involved in insulin signaling and carbohydrate metabolism and either a small upregulation or a blunted age-related downregulation of genes associated with mitochondrial function [138, 139]. One change, an increase in pyruvate dehydrogenase kinase isoenzyme 4 gene expression [139], may be particularly noteworthy, as this enzyme inactivates the pyruvate dehydrogenase complex. Inactivation of this complex is associated with increased fatty acid oxidation and a reduced reliance on carbohydrate fuels.

If these changes in gene expression translate into changes in fuel utilization during exercise, then they could have a positive effect on endurance. In fact, females are less reliant on glycolysis during sustained contractions than males [140]. This would act to preserve muscle glycogen, a limiting fuel during prolonged, submaximal exercise [141], and a stabilizer of excitation-contraction coupling in skeletal muscle cells [142]. Such a "glycogen sparing" effect has been observed during prolonged exercise in oophorectomized rats treated with estradiol [127]. These animals showed significantly greater glycogen remaining in both oxidative and glycolytic skeletal muscles, in the liver, and in the myocardium following a 2-h treadmill run. Finally, estrogen may augment glycogen storage, as muscle and liver glycogen stores are elevated during the luteal phase of the menstrual cycle [143].

Interactions Between Exercise and HT

Both exercise and HT may slow or prevent the age-related loss in muscle function that occurs after the age of 50. At the molecular level, several genes involved in energy metabolism, insulin signaling, and Ca^{2+} handling respond similarly to HT and to exercise training [138]. Compared to postmenopausal non-HT users, HT users have lower expression levels of FOXO3A, MAFbx, and MuRF-1, all enhancers of proteolysis via the ubiquitin-proteasome pathway; lower levels of myostatin mRNA, a suppressor of muscle cell growth; and higher levels of mRNAs for the muscle cell differentiation genes MyoD, myogenin, Myf5, and MFR4 and for follistatin, an endogenous myostatin inhibitor [138, 144]. A single bout of eccentric exercise shifts these proteolytic, myogenic, and growth regulatory genes in directions consistent with a more anabolic environment in all postmenopausal women [144]. However, this shift is accentuated in women on HT. All of these observations raise the important question as to whether HT augments the benefits of exercise, particularly muscle strength.

While HT may promote greater exercise-induced gains in muscle mass, most studies have found little evidence for an additive effect of HT on exercise-induced improvements in muscular strength [145–148]. Thus, while nonexercising postmenopausal women may derive a muscular strength benefit from HT, the consensus is that HT provides little if any additional strength benefits for women already engaging in exercise. Conversely, postmenopausal women not on HT may be able minimize losses in muscular strength by participating in high-impact weight-bearing (e.g., jumping) and/or resistance exercises.

Summary

Withdrawal of estrogen, either idiopathic or due to menopause, has important ramifications on the musculoskeletal system that if unopposed can increase morbidity and mortality. Osteoporosis is associated with increased fracture risk. This risk

can be reduced with weight-bearing therapies, maintaining adequate intake of calcium and vitamin D, and osteoporosis medications. Human and animal studies point to a modest, positive effect of estrogen on muscular strength, power, and endurance. The mechanisms underlying these effects are currently under investigation and may include a direct effect of estrogen on the cellular and molecular mechanisms underlying contraction and on cell energetics. Even though the effects of estrogen on muscle contractility are modest, these changes may be clinically important, particularly in fields such as rehabilitation and geriatrics.

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Chapter 13
Breast Cancer-Related Pain

Julie K. Silver and Lisa Schulz Slowman

Introduction

Pain is common in cancer, and breast cancer is not an exception. It has been reported for many years that pain is both underreported and undertreated in cancer survivors [1–3], including breast cancer survivors. In fact the estimates are that 30–50% of people undergoing acute cancer treatment experience pain and up to 70% of those with metastatic disease will have pain [4]. In addition, it has been shown that pain affects quality of life in cancer survivors [5].

Breast cancer survivors can experience a number of types of pain depending upon the management of the cancer—pain related to surgical interventions, radiation, and side effects of chemotherapy. The pain may be visceral, musculoskeletal, or neuropathic in nature. It may occur during acute cancer treatment, closely following treatment, or months to years following completion of treatment. All of these factors combined make addressing breast cancer-related pain a challenge that requires a thorough understanding of the potential etiologies, unique assessment needs, and treatment options. Of note is that breast cancer-related pain may be due to the cancer itself, metastasis, but that is not the focus of this chapter and is typically treated with opiate medications.

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Etiology/Mechanisms

Although not always possible, trying to identify the cause of pain in breast cancer survivors is essential because knowing the cause makes managing the problem easier. However, whether the cause is known or not, pain should always be adequately treated. Pain is considered the "fifth vital sign," and it requires constant vigilance by healthcare providers. Moreover, if pain is not adequately treated in the short term, it can worsen and become more difficult to control later on.

Pain seen in cancer can be characterized as somatic, visceral, or neuropathic, with each type of pain having a typical presentation:

- Somatic (also called nociceptive)—dull constant pain that increases over time
- Visceral—diffuse constant pain that is poorly localized and may be described as aching, crushing, gnawing, or cramping
- Neuropathic—cutting, piercing, or sharp pain that may be burning; it may be accompanied by paresthesias and/or weakness

Breast cancer survivors can experience all three of these types of pain. Somatic pain is often tumor-induced bone pain, which may occur with bone metastasis. Visceral pain occurs when nociceptors in the viscera are affected. In breast cancer, this type of pain may be seen in radiation-induced postmastectomy pain; it may also be experienced with metastasis to the adrenal glands (dull back pain) or liver (pain in abdomen). Finally, neuropathic pain is pain that arises from the structures of the central and/or peripheral nervous system. In breast cancer survivors, a common cause of neuropathic pain is chemotherapy-induced peripheral neuropathy (CIPN) [6].

In addition, breast cancer survivors can experience a wide range of posttreatment pain and pain syndromes which may be musculoskeletal (e.g., rotator cuff impingement), neuropathic, myofascial, or a combination thereof and may be acute, subacute, or chronic. For example, chronic postmastectomy pain may be as high as 50% [7], and radiation-induced brachial plexopathy can occur many years following radiation treatment. The incidence of shoulder pain and dysfunction (including rotator cuff dysfunction) is reported to be between <1% and 68% [8].

Following surgery, musculoskeletal pain due to decreased mobility and upper extremity use, inflammation, and scarring is common. In addition, the traction on nerves that occurs during surgical dissection (e.g., to isolate axillary nodes for excision) may cause pain and paresthesias that can last for several years [9].

Treatment-related pain and pain syndromes commonly seen in breast cancer survivors are described in the following sections.

Myofascial Pain Syndrome

Myofascial pain syndrome (MPS) is considered a regional pain syndrome that is described as having myofascial trigger points which cause (or trigger) symptoms in distant locations (see Chap. 3). The trigger points are found in palpable, inflexible

bands of skeletal muscle [10]. The pain and functional limitations a patient may experience with this syndrome vary considerably. In a prospective study examining the incidence of MPS after breast cancer surgery, researchers found that of the 116 women who completed the study, 52 (45%) developed MPS. Most of the patients in this study with MPS had active trigger points in the shoulder girdle muscles [10]. The most commonly involved muscles with active myofascial trigger points included the latissimus dorsi, serratus anterior, pectoralis major, and infraspinatus. Study participants had good control of their pain with physical therapy intervention.

Brachial Plexopathy

Radiation therapy for breast cancer patients can cause breast and arm pain, which may be due to fibrosis, neural injury, or a combination of both. Up to 9% of those who receive radiation treatment for breast cancer develop brachial plexopathy [11]. The onset of symptoms, including pain, ranges from 6 months to 20 years after treatment. Ruling out tumor recurrence is essential before diagnosing radiation-induced brachial plexopathy.

Radiation Fibrosis Syndrome

Radiation fibrosis syndrome (RFS) is a term used to describe the numerous problems that may occur after radiation treatment. Radiation therapy may injure tissue surrounding the treated region including muscle, nerve, bone, and soft tissue. There are a number of factors that can impact the development of RFS including the dose and volume of radiation, the fractionation schedule, past or concurrent treatment, genetic predisposition, and presence of comorbid conditions such as diabetes mellitus. One common characteristic of RFS is progressive sclerosis which can lead to significant pain and disability. Rehabilitation interventions, especially gentle, persistent efforts at maintaining and restoring range of motion, are critical. Botulinum toxin injections have also been studied with good results in this population [12].

Postmastectomy Pain Syndrome

Postmastectomy pain syndrome (PMPS) is characterized as a chronic pain condition that is usually neuropathic in nature. It has been described as chronic pain in the anterior aspect of the thorax, axilla, and/or arm that begins after mastectomy and persists for more than 3 months after surgery [13]. PMPS may present with pain in the arm, neck, shoulder, axilla, chest wall, or breast. Symptoms may include paresthesias, dysesthesias, allodynia, hyperalgesia, and loss of shoulder function.

Women who have a breast prosthesis implanted may be at higher risk for chronic pain. The incidence ranges from 4% to more than 50%, depending on how the pain was assessed in the various studies [14]. Risk factors associated with PMPS include age (younger patients are at higher risk), lack of a partner, and possibly greater body mass index (BMI). The presence of severe postoperative pain may also be a predictor for the development of PMPS [13].

While breast-conserving surgery (typically lumpectomy followed by radiation therapy) may seem like the solution to postmastectomy pain syndrome, this type of surgery also has a high incidence of chronic pain, especially when combined with axillary lymph node dissection. In fact, one study found a higher incidence of persistent pain in women who underwent breast conservation surgery with axillary lymph node dissection [15].

The etiology of PMPS is poorly understood, although intraoperative damage to nerves such as the intercostobrachial or axillary nerve has been suggested. Jung et al. distinguished four distinct types of chronic postmastectomy pain [16]:

1. Phantom breast pain
2. Intercostobrachial neuralgia
3. Neuroma pain (including scar pain)
4. Other nerve injury pain (including long thoracic, thoracodorsal, etc.)

PMPS is often a chronic condition. A study designed to assess the long-term prognosis of PMPS and the impact on quality of life surveyed more than 100 breast cancer survivors 6 years after having reported symptoms of PMPS in a baseline study. In follow-up, half of the women surveyed continued to complain of PMPS symptoms (at a mean of 9 years postsurgery), and those with persistent PMPS had lower quality of life scores than those whose symptoms had resolved. Risk factors for persistent PMPS in this study included younger age and heavier weight [14].

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a potential adverse effect of certain chemotherapy drugs used in the treatment of breast cancer and is the most prevalent neurologic complication of cancer treatment. CIPN can result in peripheral nerve injuries [17]. The damage can be temporary or permanent and may take up to 1–2 years to resolve following the cessation of the drug. Peripheral neuropathy develops in 50–60 % of patients treated with taxanes [18, 19], which include paclitaxel and docetaxel. Many other cancer drugs may cause neurotoxicity, including vinca alkaloids, platinum compounds, cytarabine, and thalidomide.

CIPN does not occur in all patients treated with these compounds, and the reasons for this are poorly understood. Their occurrence may be related to the particular drug, the dose, the frequency of administration, interactions with other medications, or presence of comorbidities.

Symptoms of CIPN include neuropathic pain, numbness, and paresthesias, which generally affect the feet more than the hands but can be severe in both ("stocking-glove distribution"). Symptoms may also affect the autonomic nervous system, resulting in blood pressure and heart rate fluctuations. In addition to pain, these symptoms may result in significant functional impairments such as decreased fine motor skills, postural instability, and balance problems.

Arthralgia Syndrome

The use of aromatase inhibitors (AIs) in postmenopausal women with hormone-sensitive cancer to suppress plasma estrogen levels by inhibiting the enzyme aromatase, which converts androgens into estrogens, is becoming a standard of care. As this treatment began to come into widespread use at the beginning of the twenty-first century, women began reporting new side effects, including musculoskeletal pain and stiffness, particularly involving the joints. In 2007, doctors at Dana-Farber Cancer Institute in Boston, Massachusetts, wrote the article "Aromatase Inhibitors and Arthralgias: A New Frontier in Symptom Management for Breast Cancer Survivors," [20] in which they stated, "Neither the cause, nor the time course, nor the treatment for AI-associated arthralgias is well understood" [20]. A cross-sectional study of patients receiving adjuvant AI therapy found that the onset of joint pain was generally within 3 months of beginning AI therapy and that the incidence was inversely related to the time since cessation of menstrual function. The most commonly affected joints were the wrists, hands, ankles, feet, elbows, and knees [21].

Diagnosis

There are many barriers to managing pain in breast cancer survivors. One of the most important of these is accurately diagnosing the underlying pain problem. Another is underreporting of pain symptoms by patients for various reasons. For example, patients may avoid telling their providers about painful symptoms due to the fear of losing empathy or worrying that pain may signal cancer recurrence. Therefore, clinicians need to ask specifically and systematically about pain. Assuming that a patient who does not report pain (without being asked about it) is not experiencing pain is often an erroneous assumption. Pain assessment should routinely be a component of the evaluation and reassessment of every breast cancer patient. There are a number of standardized assessment scales that can be used for evaluation of pain and its impact on function. Some of the more commonly used pain tests include the visual analog scales (VAS), Brief Pain Inventory (BPI) [22], McGill Pain Questionnaire (MPQ-SF), and the Memorial Pain Assessment Card and numeric rating scales (NRS) [23, 24]. The assessments vary in length and complexity,

Table 13.1 Pain severity

Rate how severe your pain is right now										
0	1	2	3	4	5	6	7	8	9	10
Rate how severe your pain is on your worst day										
0	1	2	3	4	5	6	7	8	9	10
Rate how severe your pain is on your best day										
0	1	2	3	4	5	6	7	8	9	10

with the VAS, NRS, and BPI being less complex and time consuming to perform. These tests have all demonstrated validity in adult populations. The key is determining which scale to use and using it consistently at each patient interaction. For example, visual analog scales (VAS) are commonly used in healthcare to quickly assess symptoms such as pain. This type of scale can be used to identify and begin to assess the severity of the pain (Table 13.1). Pain that is rated a four or more is considered “moderate” to “severe” and should be addressed.

Another type of assessment, the Brief Pain Inventory or BPI, was developed to provide information on the intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension) and has been validated by research in cancer survivors [25]. The BPI also provides information about pain relief, pain quality, and the patient’s perception of the cause of pain. The short form BPI has front and back body diagrams, four pain severity items, and seven pain interference items rated on 0–10 scales, as well as a question about percentage of pain relief by analgesics. Typically, the BPI is scored by looking at “pain severity” and “pain interference.” Patients report their pain at its “worst,” “least,” “average,” and “now” (current pain). In research trials, the items “worst” and “average” have each been used to represent pain severity.

In addition to use of standard assessments, once the presence of pain has been established, specific questions as to the nature of the pain must be asked. The location and quality of the pain provide diagnostic clues—for example, musculoskeletal pain feels different than neuropathic pain and will help to determine if the patient should be sent to physical therapy to address rotator cuff impingement (musculoskeletal pain) or back to the oncologist to discuss changes in medication to address CIPN. The patient’s description of the pain helps to improve the clinician’s understanding of the pain and can help improve treatment [1].

Assessment of pain in breast cancer survivors is not static, but rather is an ongoing process requiring ongoing assessment. Patients need to be queried about new or different pain symptoms. Clinicians should familiarize themselves with and consider all possible differential diagnoses, keeping in mind the importance of treating pain, although it may not be directly related to the cancer diagnosis.

Treatment

Pain control is an essential component of treatment for breast cancer survivors. Unrelieved pain causes unnecessary suffering and can negatively impact quality of life [26].

The World Health Organization (WHO) has developed and validated a three-step "ladder" approach to managing pain in cancer survivors [27]. This ladder is based on prescribing analgesics to treat pain in a stepwise manner, beginning with milder medications such as acetaminophen, then advancing to a more moderate analgesic such as codeine, and finally utilizing stronger opiates such as morphine. This model works well for cancer pain, but is not ideal for the types of pain most commonly encountered in breast cancer survivors. Often nonpharmacologic interventions or a combination of pharmacologic and nonpharmacologic treatment is most appropriate for this population.

The treatment of pain will be dictated by the type of pain and its etiology. For example, treatment for visceral pain due to cancer is similar to the treatments for somatic pain (with the exception of the bisphosphonate medications which are used for bone pain). The treatments for neuropathic pain due to cancer may include previously mentioned interventions as well as other classes of medications such as the tricyclic antidepressants and the antiseizure drugs. Transcutaneous electrical nerve stimulation (TENS) may also be tried. A number of other treatments, such a deep brain or spinal cord stimulation, are also under investigation and may work in select patients.

In breast cancer, as with other cancers, exercise has been shown to be beneficial for treating pain. Studies on physical activity or exercise rarely evaluate the effect of pain alone. Pain is sometimes included and often assessed with other measures such as quality of life. For example, a study titled "Impact of a walking intervention on cardiorespiratory fitness, self-reported physical function, and pain in patients undergoing treatment for solid tumors" found that in prostate and breast cancer survivors, reported pain levels went down as the exercise dose increased [28]. One study that looked specifically at physical activity in breast cancer survivors showed that physical activity was consistently associated with improved physical functioning and reduced pain [26].

In addition to general physical activity, targeted range of motion and strengthening programs can be prescribed as part of the treatment for musculoskeletal-related pain as well as the musculoskeletal components of radiation fibrosis syndrome or brachial plexopathy.

Desensitization programs can be helpful to decrease neuropathic pain components of postmastectomy pain syndrome (e.g., phantom pain, scar hypersensitivity) or radiation fibrosis syndromes. The specific aspects of the program will be dictated by the patient presentation.

The use of most physical modalities has not been well studied in cancer survivors due to the concern of exacerbating the underlying malignancy. Therefore, the modalities that are deemed "safe" or "unsafe" have little research to back up the recommendations regarding their use in this population. Recommendations regarding safety and efficacy are based on practice patterns and "standards of care."

Physical modalities that are generally deemed “safe” to use in cancer survivors include cryotherapy (e.g., the use of cold packs), biofeedback, iontophoresis, electrical stimulation (e.g., transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS)), acupuncture, and massage [29, 30]. Electrical stimulation, regardless of how it is delivered, is generally not done directly over a tumor site. The same is true for massage therapy and superficial heat.

Deep heat, including ultrasound and phonophoresis, is usually contraindicated in cancer patients, though the evidence to support this is lacking. Myofascial release, deep friction massage, and other manual techniques should be used cautiously or not at all over a site with metastasis.

In breast cancer, use of physical modalities is most commonly a component of treatment for musculoskeletal pain such as shoulder adhesive capsulitis, rotator cuff disorder, or musculoskeletal components of postmastectomy pain syndromes.

Complementary and alternative medicine (CAM) is often used in conjunction with conventional care. When it comes to using integrative therapies to treat pain, the research in this area is developing. However, to date the therapies that have been shown to have some efficacy in the treatment of pain include [31]:

- Acupuncture
- Massage
- Hypnosis
- Music therapy

Case-Based Discussion

Postmastectomy Pain Syndrome

Presentation: A 53-year-old woman 2 years status postmastectomy followed by chemotherapy and radiation. She presents with complaints of numbness in the axilla, radiating distally as well as burning pain across the chest. The pain is causing her to limit the use of her affected arm, and her shoulder is becoming stiff and sore. Because of the pain, she feels depressed and anxious and is no longer participating in her walking group.

Diagnosis: Postmastectomy pain syndrome

Treatment: Treatment consists of a combination of pharmacologic and nonpharmacologic interventions.

Pharmacologic interventions include a course of gabapentin and use of lidocaine patches topically.

Nonpharmacologic interventions include a referral to physical therapy to address the upper extremity range of motion limitations and decreased functional use and to begin a structured exercise program.

Chemotherapy-Induced Peripheral Neuropathy

Presentation: A 67-year-old woman is currently undergoing neoadjuvant chemotherapy and is planning to have a mastectomy or lumpectomy when she is finished. She presents with complaints of numbness and tingling in her hands and feet. She reports that she has fallen a number of times and is uncomfortable when standing for any length of time (e.g., when preparing dinner). She is currently on a chemotherapy regimen of doxorubicin, cyclophosphamide, and docetaxel.

Diagnosis: Chemotherapy-induced peripheral neuropathy. Docetaxel is a chemotherapeutic agent that frequently causes CIPN.

Treatment: A combination of pharmacologic and nonpharmacologic treatment is appropriate for CIPN.

Pharmacologic: There are many pharmacologic options to treat CIPN [32], including drugs given orally as well as patches and creams. Opiates have been used successfully to treat painful neuropathy [33–35]. Doctors often try nonopiate medications including acetaminophen, anti-inflammatories, anesthetics (e.g., topical lidocaine as a patch or a cream), antiseizure drugs (e.g., pregabalin, gabapentin), and antidepressant drugs (e.g., tricyclic antidepressants).

Nonpharmacologic: Referral to physical therapy to address balance and postural stability issues is appropriate. Referral to occupational therapy to address upper extremity functional deficits and use of adaptive equipment (e.g., stress pads to stand on in the kitchen, large-handled utensils) may be appropriate as well.

Arthralgia Syndrome

Presentation: A 48-year-old woman with new complaints of wrist, ankle, and knee pain. She recently started taking an aerobics class and has returned to work in retail sales where she is on her feet most of the day. She is considering stopping work and dropping out of her aerobics class because of the pain, fearing either that she has started to do too much too quickly or that she has had a recurrence of her breast cancer and it has metastasized. Her oncologist recently started her on anastrozole.

Diagnosis: Arthralgia syndrome. Anastrozole is an AI. AIs have been linked to development of arthralgias.

Treatment: Symptoms can often be managed with a combination of lifestyle changes (e.g., weight management, weight-bearing exercise, joint protection) and pharmacologic interventions.

Pharmacologic: Acetaminophen and nonsteroidal anti-inflammatory are first-line drugs. If continued symptoms, may progress to tramadol and opiates. Other medications such as nortriptyline, gabapentin, and pregabalin may be considered as well.

Nonpharmacologic: Instruction in lifestyle changes, referral to physical therapy for graded exercise program, and instruction in joint protection.

Conclusion

The physical and psychological effects of cancer pain can be overwhelming. Pain negatively impacts quality of life and increases feelings of helplessness, as well as anxiety and depression. It interferes with the ability to engage in normal activities including home, work, and recreational and social commitments. Being aware of the types of pain experienced by breast cancer survivors, understanding the etiologies of the pain, and knowing appropriate treatment interventions to manage the pain are critical in improving outcomes for breast cancer survivors.

Patient Resources

Reach to Recovery ® (American Cancer Society Program)

800-ACS-2345
cancer.org

The Reach to Recovery ® program helps patients with breast cancer cope with their diagnosis, treatment, and recovery. The volunteers in this program are breast cancer survivors trained to share their knowledge and experiences in a supportive manner. Ongoing support groups are available.

Susan G. Komen Breast Cancer Foundation

5005 LBJ Freeway, Suite 250
Dallas, TX 75244
800-IM-AWARE (800-462-9273)
komen.org

The Susan G. Komen Breast Cancer Foundation funds research grants and supports education, screening, and treatment projects in communities around the world. In addition to information about breast cancer, the website contains information about obtaining grants, making donations, participating in events, subscribing to free newsletters, and purchasing gifts and educational materials from the foundation.

Breastcancer.org

111 Forrest Ave.
Narberth, PA 19072
610-664-1990
breastcancer.org

Breastcancer.org is a nonprofit organization that provides information about breast cancer. In order to facilitate the decision-making process, breastcancer.org helps women and their families make sense of complex medical and personal information about breast cancer. In addition to information about prevention, symptoms and diagnosis, treatment, recovery, and support, the website offers monthly online conferences with breast cancer experts and monthly reports on breakthroughs in breast cancer research.

Y-ME National Breast Cancer Organization

212 W. Van Buren, Suite 1000
Chicago, IL 60607-3908
800-221-2141
800-986-9505 (Spanish)
312-986-8338
y-me.org
y-me.org/Spanish.htm (Spanish)

Y-ME provides information and support to people with breast cancer and their families. In addition to a national hotline, the organization's website has a wealth of resources that covers everything from understanding the disease to finding support groups to locating wigs and prostheses. Information is also available in Spanish.

Lance Armstrong Foundation (LAF)

P.O. Box 161150
Austin, TX 78716-1150
512-236-8820
laf.org

The LAF was founded in 1997 by cancer survivor and champion cyclist Lance Armstrong. This foundation provides the practical information and tools people living with cancer need to survive. LAF's mission is to inspire and empower people with cancer.

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Chapter 14
Physical Therapy for Female Pelvic Pain

Jessica McKinney

Introduction

The purpose of this chapter is to discuss the role of physical therapy in the management of women with pelvic pain disorders. Pelvic pain is a costly, prevalent, yet poorly understood condition, found to disproportionately affect women 4:1 [1]. Annual healthcare costs in the US are estimated in excess of $880 million for physician visits alone, and nearly three billion when out-of pocket expenses and mental health visits are included [2]. Prevalence of pelvic pain is found to be similar to prevalence rates of asthma and low back pain [3], and the 3-month prevalence of chronic pelvic pain is estimated at 24% [4]. The majority of prevalence studies of pelvic pain have excluded women with vulvar pain disorders, as well as women who were pregnant or who had been pregnant within the past year. Therefore, the prevalence of all pelvic pain conditions is likely greater than that commonly cited in the literature. For example, an investigation by Harlow and Stewart identified a 16% lifetime prevalence of unexplained chronic vulvar pain, equating to approximately 14 million US women; a much higher prevalence than that found in earlier studies [5]. This high prevalence of female pelvic pain and the changing healthcare landscape are contributing to the now widely accepted and promoted concept of a multidisciplinary and collaborative approach to diagnosis and treatment that includes physicians of multiple specialties, physical therapists, and mental health professionals [6, 7].

Physical therapists specializing in women's health first organized within the American Physical Therapy Association in 1977 as the Section on Obstetrics and Gynecology, later renamed the Section on Women's Health in 1994 [8]. Since then, interested physical therapists have worked with a variety of healthcare providers to

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develop the knowledge and skills to treat women affected by breast cancer, osteoporosis, impairments brought on by pregnancy, postpartum rehabilitation, and disorders of the pelvis including pelvic pain, incontinence, and sexual, voiding, and defecation dysfunctions. A full description of the role of physical therapy in treating these health issues is beyond the scope of this chapter. This chapter will, however, reveal how physical therapists may be an integral part of a multidisciplinary approach to the evaluation and treatment of pelvic pain in women.

Etiology

There have been attempts in recent years to identify risk factors for the development of female pelvic pain. Many of the following conditions or historical elements are commonly associated with pelvic pain: endometriosis, pelvic adhesions, irritable bowel syndrome, genitourinary dysfunction, depression and sleep disorders, and a history of childhood sexual or physical abuse [9–15]. However, psychological distress and sleep disorders may be consequences of chronic pain rather than antecedent conditions [16]. In one systematic review of 122 chronic pelvic pain studies, strong and consistent associations were noted between chronic pelvic pain and the presence of pelvic pathology, a history of abuse, and coexistent psychological morbidity [10].

In a comparison of musculoskeletal (MSk) physical exam findings in female subjects with chronic pelvic pain versus non-symptomatic controls, case subjects had a higher frequency of abnormal findings on a number of external pelvic, low back, and abdominal exam parameters, including tests of pelvic girdle instability. In addition, case subjects had a high frequency of tender points on palpation of the pelvic floor musculature, whereas the majority of control subjects were non-tender on pelvic floor examination [17]. This study confirms a high-degree of musculoskeletal involvement in women with chronic pelvic pain. Researchers are also investigating the association of lumbopelvic pain with disorders of continence and respiration [18].

As the experience of pregnancy and childbirth remains uniquely female, and women are disproportionately affected by pelvic pain, the genesis of pelvic pain may well be linked to both the predictable and the traumatic physical consequences of childbearing. A thorough and thoughtful investigation of this potential relationship is warranted.

One system for classifying the etiology of pelvic pain described in the literature is that of a primary versus secondary dysfunction [17, 19–22]. Consideration of pelvic pain that is "primary" compared to that which is "secondary" is a helpful model to employ when investigating individual etiology and determining course of care. Primary pelvic pain or pelvic floor dysfunction results from a known incident, trauma, or disease process of the bony pelvis, its soft tissue structures, or the pelvic viscera. Examples of this include tissue trauma experienced during childbirth, pain that develops after gynecological surgery, or pain associated with infection or local inflammation (see Case Study 2). Secondary pelvic pain or pelvic floor dysfunction applies to

individuals for whom pelvic pain developed and progressed insidiously, frequently present in the face of negative standard diagnostic testing (see Case Study 1).

Consider for example, that the pelvic floor musculature is known to tighten as a subconscious response to emotional stress, anxiety, or fear [23]. When unrecognized by the individual this physical manifestation of one's emotional state can ultimately lead to tension of the pelvic floor, where the chronic holding pattern of the muscle deprives the tissue of blood, oxygen and nutrients. This can lead to ischemic pain with trigger points and decreased functional range of motion (ROM). This continuous muscle tension leads to further functional impairments relative to pain, continence, respiration, pelvic stability, and sexual function [16, 17, 21, 24, 25].

The pelvic floor has a dilative function that is required for uncomplicated vaginal childbirth [26]. It is also largely responsible for maintaining continence, which it does through a baseline of muscle tone that is maintained during bladder filling and through rapid strong contractile force that prevents leakage during sudden increases in intra-abdominal pressure (IAP) (i.e. cough, sneeze, position change) [26, 27]. In addition, the pelvic floor structures contribute powerfully to normal sexual arousal and function [28].

To add to the complexity, from a musculoskeletal standpoint, the primary requirement of the pelvis is transfer of load between the lower extremities and trunk, and against the pull of gravity [29–32]. The pelvic floor is involved in the balance between stability and mobility required by the pelvis for optimal function in accordance with load transfer requirements [33–37]. It does this by direct fascial connections and attachments to the bony pelvis, and through indirect synergistic relationship with muscles widely noted for trunk stability [36]. When the pelvic floor musculature and fascia is considered, it can be appreciated that the healthy pelvic floor is vital in support of the pelvic viscera against gravity and against increases in IAP.

Recent literature identifies the muscles of the "core" as a synergistic unit for lumbopelvic stability, comprised of the diaphragm, transverse abdominals, deep multifidus, and pelvic floor [21, 31, 32]. This unit functions subconsciously and prior to body movements and is thought to pre-load the system in order to protect against excessive loading of the spine, pelvis, and pelvic contents during physical activities. Lumbar pain has been shown to disrupt this normal functioning [38–41]. Interestingly, this function does not recover spontaneously with pain resolution [38, 42]. Therefore, as pain improves, the individual returns to everyday activities, all the while utilizing suboptimal muscle firing patterns. These faulty compensation strategies may then perpetrate their own dysfunction, resulting in pain due to overuse of certain muscles and atrophy from underutilization of others.

Physical Therapy Evaluation

There is consensus among many experts in the field of pelvic pain that the processes of central and peripheral sensitization (see Chap. 2) and dysfunction of the musculoskeletal system (see Chap. 5) play a strong role in the development and

perpetuation of symptoms [7, 19, 43, 44]. Physical therapists are trained in the evaluation and treatment of dysfunction of the musculoskeletal system, such as disorders of posture, movement, and function. The high prevalence of musculoskeletal findings observed in women with chronic pelvic pain has led some authors to suggest that the women's health physical therapist play an early role in their evaluation [20, 22]. This allows the physical therapist to contribute by determining the degree of musculoskeletal involvement, providing recommendations on appropriateness of physical therapy as an intervention, and if necessary, commencing physical therapy to address dysfunction even while other medical consultations, evaluations, and interventions are being explored [20, 22].

History

A thorough subjective history is essential to determine the etiology of a patient's pelvic pain and will guide the evaluative process. In all cases, standard questioning entails a description of the characteristics and location of the pain, exacerbating and relieving factors, obstetrical history (including instrument-assisted deliveries, episiotomies, number and types of deliveries), previous pelvic surgeries or other clinical and surgical treatments, as well as any history of pelvic inflammatory disease. Information regarding problems within the gastrointestinal, urinary, and reproductive systems should be obtained, including history of dyspareunia, dysmenorrhoea, and menstrual patterns. History of orthopedic dysfunction, particularly with regard to the lumbar spine, pelvis, hips, and lower extremities is very important, including any symptoms that persist at the time of evaluation for pelvic pain. Psychosocial history should also be obtained: past or present traumas, including domestic and/or sexual abuse; depression; anxiety, or other psychosocial disorders.

Examination

Several publications have looked at the prevalence of MSk findings in women with pelvic pain using a variety of techniques and classification systems. Spitznagle described a classification system developed by Shirley Sahrmann that organizes impairments into diagnostic categories, allowing for a systematic approach to pain syndromes [45, 46]. Haugstad et al. describe findings of Mensendieck-trained physical therapists performing a standardized examination of posture, movement, gait, sitting posture, and respiration [47]. An additional study by Tu et al. [17]. and reports by Rosenbaum and Owens [24] and Prendergast and Weiss [48] discuss several musculoskeletal parameters that are commonly evaluated by physical therapists including posture, pelvic stability, hip range of motion, flexibility and tenderness in pelvic girdle muscles, and pelvic floor examination. While there are descriptive differences among these authors, what remains consistent is the high incidence of MSk dysfunction identified by each with regard to pelvic pain populations.

Another systematic approach for identifying MSk, postural, biomechanical, and neurological dysfunction is taught by the North American Institute of Orthopedic and Manual Therapy and begins with an upper or lower quadrant-scanning exam [49–51]. The scan incorporates a majority of the parameters suggested by other authors and helps the physical therapist quickly identify any cautionary items that would require further medical consult, indicating that the individual is inappropriate for physical therapy at that time. In light of the increased prevalence of physical therapists as a point of entry into the healthcare system, their ability to skillfully identify patients with more concerning symptoms is critical, as is their ability to refer and communicate appropriately with physicians and other healthcare providers. Table 14.1 provides a description of the lumbar screening exam. Table 14.2 describes the additional recommended MSk tests described in the literature in the assessment of pelvic pain.

Table 14.1 NAIOMT lumbar scan

Scan sections	Section components
Observation	(a) Changes in structure/architecture (sitting, standing) Scoliosis Postural shifts Increased/decreased spinal curvatures (b) Local signs Skin color, texture, scars, etc. Soft tissue contours from atrophy, hypertrophy, edema, etc. (c) Neurological Gait Motor control (spasticity, coordination, balance) Brain/brainstem/neurovascular (dysphagia, dysarthria, eye tracking, communication, facial palsy, etc.) (d) Antalgic gait or postures, general willingness to move
Lumbar movements (flexion, extension, side-bending, rotation)	(a) Active range of motion (AROM) (b) Overpressure applied at end range AROM (c) Resistance applied to movement (toward neutral from end range AROM)
Neurologic	(a) Dural testing Slump test Slump with bilateral straight leg raise (knee ext, dorsiflexion) Straight leg raise (SLR) Well leg SLR (crossed or contralateral SLR) Femoral nerve mobility (b) Key muscle test (Motor) L2 through S2 (c) Reflexes Deep tendon reflexes (DTR): Patellar, Tibialis anterior, Medial hamstrings, Extensor digitorum, Achilles Upper motor neuron tests: Babinski, Oppenheimer, Clonus (d) Dermatome (Sensory) L1 through S3/4

(continued)

Table 14.1 (continued)

Scan sections	Section components
Provocation	(a) Lumbar compression and traction (b) Prone torsion test (c) Posterior-anterior compression (performed segmentally)
Vascular	Femoral, Popliteal, Dorsalis pedis arteries[a]
Layer palpation (through lumbopelvic region)	(a) Identify pain or muscle reactivity (trigger points, tone)[b] (b) Atrophy/inhibition of segmental or global muscles
Screen/scan	
(a) Sacroiliac joint scan (b) Lower extremity scan (as indicated by history and findings)	(a) SIJ PSIS in flexion (asymmetry, Fortin's finger test) Kinetic step test (March test) SI gapping (posterior stress test) SI compression (anterior stress test) Torsion (stress ilium into ant/post rotation) (b) Hip Active/overpressure/resisted motion for all flexion, extension, abduction, adduction, internal rotation, external rotation Scour test FABER/FADIR tests Knee Active/overpressure/resisted motion for flexion, extension, hyperextension ER/IR at 90° Scour Quadrant combined motion tests Ankle Active/overpressure/resisted motion for plantarflexion, dorsiflexion, inversion, eversion
Special tests (as indicated by history and findings)	(a) Combined motion testing for lumbar spine ("H" and "I", standing) Extension and side-bending Flexion and side-bending (b) Peripheral joint weight-bearing scan Squat Climbing test Axial rotation Walking (c) Compression and traction (sitting and standing) (d) Palpation of abdominal aorta (e) Kidney percussion (f) Abdominal quadrant

References: [49–51]
[a]Performed as indicated by the history
[b]See specific muscle list in Table 14.2

Table 14.2 Additional recommended components of musculoskeletal exam for pelvic pain

Additional examination for pelvic pain	Examination components
General observations	Facial pain characteristics
	Body language
Specific postural observations	Standing
	Habitual base of support
	Orientation of pelvis in space
	Orientation of shoulders and upper back relative to pelvis
	Sitting
	Habitual amount of hip/knee flexion
	Habitual crossing of legs
	Position of lumbar curvature
	Symmetry of loading on ischial tuberosities
	Dynamic
	Crossed syndrome patterns (as described by Janda, Keyes)
	Trendelenburg (gluteus medius weakness/decreased function)
Diastasis recti	Note finger breadths inserted between the medial rectus abdominus muscle with neck flexion 2 in. above the umbilicus, at the umbilicus, and 2 in. below the umblicus
Active straight leg raise	Performed with or without stability belt to assess form/force closure of the pelvic ring
Firing sequences of major muscle groups	Janda's hip extension and hip abduction tests (1983)
Respiration	Patterns of respiration
	Diaphragm and rib position, mobility, excursion
	Capnometry can be used to quantify for evaluation and use as biofeedback tool
Specific muscles for palpation	Examining for length, strength, and trigger points
	Multifidi, iliopsoas, abdominals (all), femoral adductors, piriformis, obturator externus, gluteals (all), quadratus lumborum, latissimus dorsi, hamstrings, quadriceps

References: [17, 21, 47, 71–73]

Connective tissue findings common among individuals with pain conditions, particularly findings relevant to pelvic pain are well described in the literature [52, 53]. These consist of trophic changes, increased resistance to mobilization, and increased skin sensitivity with mobilization. They are found in predictable areas of the dermis commonly referred to as "cutaneous referral zones of the pelvic floor" and "Head's zones", after the physician Sir Henry Head, who in 1893 described areas of cutaneous involvement in association with various visceral pathologies

[54]. The mechanisms behind this have yet to be fully elucidated, but their presence has been consistently demonstrated in animal models and is thought to be due to viscerosomatic convergence (see Chap. 2) and the heavy influence of the autonomic nervous system throughout the pelvis [55].

It is now widely accepted that examination of the pelvic floor musculature is a key element of the evaluation of women with pelvic pain. The comprehensive pelvic floor exam should provide information about neurological structures, motor control, and muscle integrity. Many evaluation schemes and instruments have been used and investigated, but vaginal palpation remains the most recommended and reliable [22]. Several approaches are described in the literature and significant agreement exists regarding the following components.

External observation of the perineum is first performed and overall impression is noted. This should include visualization and examination of all perineal scars for mobility and sensitivity. Palpatory internal examination includes observations of the tone, tenderness, and presence of trigger points or taut bands in the entire musculature of the pelvic floor, with particular emphasis on the levator ani, ischiococcygeus, and arcus tendineous of the levator ani, obturator internus and piriformis. This is usually performed via single digit manual exam. Measurements of strength are also obtained via digital manual exam and are graded by the examiner according to a 0–5 manual muscle testing (MMT) scale, where "0" represents complete loss of muscle function and "5" represents maximal strength [56]. Further description of pelvic floor MMT and assessment of additional factors, such as endurance and fast twitch muscle activity are described in detail elsewhere in the literature [57, 58]. Recent literature is also exploring the potential development and use of a pelvic floor muscle coordination scale [59].

Historically, emphasis on pelvic muscle strength has focused on the ability of an individual to perform a pelvic muscle contraction. In 1954, it was Dr. Arnold Kegel, who first suggested that pelvic floor squeezing exercises could be effective in decreasing postpartum incontinence. However, many publications and clinicians now assert that findings of weakness in squeeze strength can be the result of pelvic floor muscles that are shortened and too tight to contract effectively. Therefore, a program solely based on strengthening of such musculature would be counterproductive and may actually worsen symptoms. Attention is given not only to contraction strength but also the ability of the individual to relax after contraction. Delayed or incomplete relaxation, even in the presence of a weak contraction, is indicative of short, tight muscles that are lacking in motor control, range of motion, and likely compromised by trigger points. This condition must be fully resolved before traditional strengthening can occur.

Treatment

There is no uniform physical therapy treatment plan that is applicable for all patients and the most successful plan will be tailored to the individual's needs, based upon their history, objective examination findings, and personal goals for therapeutic

outcomes. The following is a brief description of the scope of physical therapy treatment interventions that may be helpful in the treatment of female pelvic pain.

Education

Clinical experience suggests that many women presenting for treatment of pelvic pain have very little knowledge of the anatomy and function of the pelvis. Time dedicated to education on and discussion of these topics, with the aid of anatomical models, texts, and mirrors is necessary and will help motivate the patient to be an active participant in her course of care.

Manual Therapy

The practice of manual therapy is one of the most common used by physical therapists treating pelvic pain. There are many organizations dedicated to the teaching and study of a variety of manual therapy techniques. Manual therapy interventions include joint mobilizations and manipulations intended to restore normal mobility at hypomobile joints and gentle mobilizations that can decrease inflammation at irritable joints [60]. Soft tissue techniques are widely used and include general mobilization techniques for muscles that are adaptively shortened and more specific techniques for release of trigger and tender points [43, 61–63]. Techniques for detecting restrictions in and mobilizing connective tissue, including restrictions in the dermis, have been described well in the literature and are noted to be especially useful in the treatment of individuals with pelvic pain who exhibit the trophic and connective tissue changes earlier described [52, 53]. Visceral mobilization is another useful tool for physical therapists treating pelvic pain due to the number and proximity of organs in the pelvis and lower abdomen and the previously noted phenomenon of viscerosomatic convergence, as well as the presence of scar tissue when there is a history of abdominal surgery [64]. External or vaginal scar tissue is also responsive to manual therapies. Knowledge of the phases of healing and use of scar mobilization techniques promote proper tissue remodeling in early phases and can improve mobility of scar tissue and adhesions that are chronic [61].

Nervous system innervation of the female pelvis is plentiful and peripheral nerves in this region are vulnerable to injury during labor and delivery, abdominopelvic surgeries, or in the setting of chronic valsalva due to bowel and/or bladder dysfunction. Adverse neural tension is defined as “abnormal physiological and mechanical responses produced from nervous system structures when their normal range of movement and stretch capabilities are tested” [65]. Typical symptoms are burning, itching, stabbing, or electrical sensations which can persist even after the aggravating stimulus is removed. Since neural structures cannot be stretched, neural mobilizations are used to lengthen the nerve in one location while shortening it in another [48, 65].

Exercise

The physical therapy evaluation will identify areas of weakness and inability to recruit key muscles in the trunk, pelvis, and lower extremities and treatment should focus on restoring proper strength and function. This includes, but is not limited to pelvic floor muscle strengthening and relaxation exercises. Specific patterns of muscle weakness and inhibition are common in individuals who have experienced lower back pain and many of these patterns are also detected in individuals with pelvic pain syndromes [66]. Prescriptive therapeutic exercises and neuromuscular re-education exercises are used to address these findings.

Dynamic and static stretching exercises are frequently incorporated into the treatment plan for women with pelvic pain. As with all exercise and intervention, this should vary somewhat according to the individual's needs. However, flexibility training of the following muscle groups is frequently employed: hip flexors, hip rotators, quadratus lumborum, thoracolumbar paraspinal muscles, and the latissimus dorsi.

Cardiovascular exercise should be incorporated into the treatment plan. This provides benefits for general health and fitness, as well as for pain tolerance due to its influence on production of endogenous opioids [67]. Many women with pelvic pain demonstrate decreased activity levels and guidance from the physical therapist is beneficial to find appropriate modes, frequency, and intensity of cardiovascular exercise in order to reap these benefits.

Biofeedback and Electrotherapy

Biofeedback is widely used as an intervention in treatment of female pelvic pain, frequently through the use of external or internal (vaginal or anal) surface electromyography to monitor pelvic floor muscle tone in the treatment of pelvic floor hypertonus disorders [68]. Also emerging as a valuable biofeedback tool is the use of therapeutic ultrasound to visualize the pelvic floor muscles and their response to intentional contraction or relaxation [69]. In both therapeutic ultrasound imaging and sEMG, the information provided can help women learn to identify, coordinate, and relax the muscles of the pelvic floor. Electrotherapeutic modalities are used by physical therapists to elicit muscle contractions or for pain modulation. Recommended equipment and electrical stimulation parameters are described elsewhere in the literature [70].

Behavioral

The literature indicates that individuals with chronic pelvic pain demonstrate aberrant movement patterns, postural dysfunction, and poor compensatory strategies for dynamic and static pelvic stabilization [47]. To ensure optimal outcomes, the patient

must become aware of her faulty movement patterns and change her behavior so that poor strategies and habits are no longer reinforced. This may include workspace evaluations, observations of driving setup, and assessment of proper mechanics for transitional movements, lifting, and carrying, as well as static standing and sitting posture.

Habits specific to pelvic floor function will likely need to be addressed. It is not uncommon to see complaints of voiding or defecatory dysfunction in individuals with pelvic pain. This requires a discussion of proper bowel and bladder habits, including dietary irritants, timed voiding and fluid titration, and toileting position. Behavioral changes frequently need to be addressed relative to sexual activity. For example, the woman with positional dyspareunia can be provided with suggestions on alternative positions. Improved control over pelvic floor muscles may also help women with dyspareunia to decrease pain during sexual arousal and activity.

Patients should be educated regarding pelvic floor muscle tightening in response to stressful and anxiety-producing situations. Teaching specific stress management techniques such as deep breathing and conscious muscle relaxation exercises may be useful.

Cases

Case 1

A 49-year-old woman was referred to physical therapy for 3 years of insidious onset and progressive vulvar pain and irritation. Initially, she treated these symptoms with over-the-counter anti-fungal medications. Symptoms resolved, but resurfaced a few weeks later. Irritation continued to appear and remit without response to repeated anti-fungal treatment and despite negative cultures. She described her pain as raw, irritating, itching, and burning. Her pain was frequently aggravated by sitting and driving, vigorous exercise, and had become nearly prohibitive for sexual activity. Additional history included three uncomplicated vaginal deliveries, no abdominal or gynecological surgeries, mild stress urinary incontinence, herniated disc at L5-S1 6 years prior, and no history of trauma. She reported back pain that occurred occasionally, particularly with increased levels of physical activity.

Physical therapy findings included mildly increased lumbar lordosis, narrow base of support, and increased tone in posterior hip musculature, particularly in the hip external rotators. Trunk active range of motion was limited in extension and side-bending, demonstrating discomfort, apprehension, and a deep skin crease at L5-S1 with the former movement. Neurological tests were normal. Hip mobility restrictions were identified in extension, adduction, and internal rotation. Standing tests for pelvic mobility and stability demonstrated poor dynamic stability of the sacroiliac joint in one leg stand. Palpatory exam revealed segmental atrophy of the deep lumbar multifidus at L5-S1 and S1-S2 on the right (the side of the previous disc herniation), as well as increased muscle tone with presence of trigger points in the right piriformis, gluteus minimus, gluteus medius, and obturator muscles.

Segmental stability testing of the lumbar spine revealed hypermobility in the transverse plane at L5-S1. Active straight leg raise test revealed difficulty elevating the right lower extremity and was improved with both posterior and anterior pelvic compression. A three-finger breadth diastasis recti was identified at all manual measurement points: 2 in. above, at, and 2 in. below the umbilicus.

Pelvic floor exam revealed reproduction of burning pain with light touch of the introitus. Weak pelvic muscle concentric contraction strength and delayed relaxation after contraction was detected. Endurance of muscle contraction was poor and strength of squeeze and ability to relax decreased with repeated contractions. Increased muscle tone, tenderness to palpation, and trigger points were present throughout the pelvic floor, particularly in the right levator ani and obturator internus.

Assessment indicated progressive deterioration in dynamic and static pelvic stabilization strategies secondary to inhibition of the deep core muscles of transversus abdominus and multifidus at L5-S1. This was felt to be due to unresolved diastasis recti abdominus (DRA) secondary to pregnancy, which created structural compromise, as well as inhibition of TrA and multifidus, which had persisted following lumbar injury. A faulty stabilization strategy consisting of over-recruitment of the posterior hip muscles, in particular the hip external rotators was observed. This included obturator internus, a synergist of the levator ani through functional relationships and shared fascial attachments, whose posterior margins mark the entry point of the pudendal nerve into the pelvis at Alcock's canal. Over-recruitment of the hip external rotators frequently results in shortening and tightening of the pelvic floor muscles via their synergistic relationship. In our patient, this compromise led to chronic holding patterns, creating pelvic floor muscle ischemia, the presence of myofascial trigger points, and nervous system sensitization (see Chap. 5). This perpetuated the feeling of vulvar irritation and pain in the absence of actual infection or ongoing injury.

Treatment consisted of patient education regarding the findings and on proper postural and stabilization strategies. Manual therapy techniques were employed to restore proper muscle length and resolve trigger points in the posterior hip and pelvic floor muscles. Motor control exercises were used to facilitate transverse abdominals and deep lumbar multifidi, followed by progressive muscle strengthening exercises. Mind-body strategies and breathing exercises were taught to promote muscle awareness and reduce stress-associated muscle tightening. Education was provided on strategies for sexual activity for improved control over vulvar pain response. Finally, restoration of proper posture in sitting, standing, and with functional and recreational tasks was incorporated, as were exercises for global strengthening, stability and conditioning.

The patient learned co-contraction of her transversus abdominus, multifidus, and pelvic floor. DRA resolved to </= 1 finger width separation at all measurement points. Active straight leg raise was negative with TrA/MF/PF co-contraction. Minimal to no pain was provoked with palpation of vulvar tissue. Pelvic floor ROM was within normal limits and squeeze strength was good with efficient relaxation after contraction. The patient reported overall decreased pain level and less frequent exacerbations. Also, when symptoms occurred, she was able decrease her pain level

further by incorporating breathing and muscle relaxation techniques. In addition, she was able to resume a regular exercise program which included cardiovascular activity, strength training, and yoga, as well as sexual activity including vaginal intercourse with minimal to no pain symptoms.

Case 2

A 36-year-old woman presented to physical therapy with a chief complaint of painful intercourse since the birth of her only child 5 years prior. She reported a history of significant vaginal tearing following a long and difficult labor requiring “a ton” of stitches. Vaginal pain persisted early postpartum with sitting, walking, and bowel movements. She attempted intercourse at 7 weeks postpartum and was unable to tolerate entry secondary to pain. Upon discussion with her gynecologist she was told that her trauma with delivery was significant and that it could take up to several months for sexual activity to normalize.

By 9 months postpartum she reported ongoing pain with vaginal penetration, rated as an 8–9/10 in severity on visual analog scale. She was unable to achieve orgasm and experienced local vaginal and diffuse pelvic pain for 3–4 days following intercourse. She sought further advice from her gynecologist at this time and was told to use additional lubricant and that sometimes things change permanently after childbirth. For four additional years there was no improvement in symptoms. Upon advice from a friend she finally did consult another physician and a pelvic floor physical therapist.

Physical therapy findings included increased thoracic kyphosis, decreased lumbar lordosis, and posterior pelvic tilt. These postural findings have been described by some authors as common in women with chronic pelvic pain due to protective guarding and tightening of pelvic muscles [45, 46, 56]. Trunk and hip ROM were normal and pain-free. Neurological exam was normal. Decreased dynamic sacroiliac joint stability was noted bilaterally. No DRA was present.

Pelvic floor exam revealed visible perineal scar and shortened distance between the introitus and perineal body. Gentle manual exam detected a thick, rope-like scar extending 6 cm into the vagina. The scar was maximally resistant to mobilization and maximally tender with gentle pressure and with attempted mobilization. Pelvic floor muscle recruitment was negligible and marked substitution with the gluteals and adductors was noted. Trigger points were present in the entire musculature of the pelvic floor bilaterally. No pudendal nerve findings were present.

Interventions included patient education and instruction in self-mobilization of perineal and vaginal scar tissue. Manual therapy techniques were used for trigger point release of the pelvic floor muscles and graded scar mobilization. Therapy progressed to include postural re-education, therapeutic exercise, specific education regarding foreplay and positioning with instructions to return to full level of desired sexual activity.

At the conclusion of 9 months of physical therapy, scar mobility had improved to within normal pain-free limits. All trigger points were resolved. Pelvic floor range

of motion was restored and strength greatly improved. Sitting and standing posture demonstrated neutral pelvic position. Sexual activity had returned to desired levels and was pain-free.

Resources

Finding a Physical Therapist

The American Physical Therapy Association (APTA) maintains a database of members that is organized by self-declared area of clinical specialty or interest and by geographical region (www.apta.org, select "Find a PT"). The Section on Women's Health, a division of the APTA, also has regional representatives who have information on contacting physical therapists who are specifically members of this section (www.womenshealthapta.org).

There are several organizations involved in training physical therapists in various areas of women's health and pelvic floor dysfunction. One of these, The Pelvic Rehabilitation Institute, features an online physical therapist directory of individuals who register with their site as physical therapists trained in pelvic floor examination and treatment (www.pelvicrehab.com).

Training for Physical Therapists

The afore-mentioned organizations, the Section on Women's Health of the American Physical Therapy Association and The Pelvic Rehabilitation Institute, both offer sequential training and certifications in pelvic floor, obstetrics, and specialty courses related to these topics. Topical online searches for "manual therapy" and "orthopedic manual therapy" will lead to a number of organizations that offer paths to certification or individual training courses. In addition, various organizations such as the International Pelvic Pain Society coordinate conferences and specialty courses that are beneficial to providers involved in the treatment of pelvic pain.

Conclusions

The importance of a comprehensive and multidisciplinary approach to management of pelvic pain is overwhelmingly recommended, as is the role of physical therapists as part of this team. Physical therapists contribute through their ability to evaluate the structural, biomechanical, postural, functional, musculoskeletal, and neurologic dysfunctions that may cause, perpetuate, or result from pelvic pain. Physical therapy

involvement at early stages of pelvic pain is highly recommended. Rehabilitative interventions include connective tissue manipulation, behavioral retraining, and education for posture, activity, bowel and bladder habits, therapeutic exercise, neuromuscular re-education, and manual therapy techniques for joints, soft tissue, and fascia. Physical therapy appears to be most successful when all these elements are considered and positive findings addressed through a progressive and individualized treatment program.

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